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1. Identify the histologic types and prognostic models used for mantle cell lymphoma
2. Explain the different options for initial therapy for mantle cell lymphoma
3. Explain the different options for treatment of recurrent mantle cell lymphoma

Activity Disclosures

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ANNUAL CLINICAL UPDATES IN HEMATOLOGICAL MALIGNANCIES:
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Mantle cell lymphoma: 2013 Update on diagnosis, risk-stratification, and clinical management

Julie M. Vose*

***Disease Overview*: Mantle cell lymphoma (MCL) is a non-Hodgkin lymphoma characterized by involvement of the lymph nodes, spleen, blood, and bone marrow with a short remission duration to standard therapies and a median overall survival of 4–5 years.**

***Diagnosis*: Diagnosis is based on lymph node, bone marrow, or tissue morphology of centrocytic lymphocytes, small cell type, or blastoid variant cells. A chromosomal translocation t(11:14) is the molecular hallmark of MCL, resulting in the overexpression of cyclin D1. Cyclin D1 is detected by immunohistochemistry in 98% of cases. The absence of SOX-11 or a low Ki-67 may correlate with a more indolent form of MCL. The differential diagnosis of MCL includes small lymphocytic lymphoma, marginal zone lymphoma, and follicular lymphoma.**

***Risk Stratification*: The Mantle Cell Lymphoma International Prognostic Index (MIPI) is the prognostic model most often used and incorporates ECOG performance status, age, leukocyte count, and lactic dehydrogenase. A modification of the MIPI also adds the Ki-67 proliferative index if available. The median overall survival (OS) for the low risk group was not reached (5-year OS of 60%). The median OS for the intermediate risk group was 51 months and 29 months for the high risk group.**

***Risk-Adapted Therapy*: For selected indolent, low MIPI MCL patients, initial observation may be appropriate therapy. For younger patients with intermediate or high risk MIPI MCL, aggressive therapy with a cytarabine containing regimen ± autologous stem cell transplantation should be considered. For older MCL patients with intermediate or high risk MIPI, combination chemotherapy with R-CHOP, R-Bendamustine, or a clinical trial should be considered. At the time of relapse, agents directed at activated pathways in MCL cells such as bortezomib (NFkB inhibitor) or lenalidamide (anti-angiogenesis) are approved agents. Clinical trials with Ibruitinib (Bruton's Tyrosine Kinase inhibitor) or Idelalisib (PI3K inhibitor) have demonstrated excellent clinical activity in MCL patients. Autologous or allogeneic stem cell transplantation can also be considered in young patients. Am. J. Hematol. 88:1083–1088, 2013. © 2013 Wiley Periodicals, Inc.**

Disease Overview

Mantle cell lymphoma (MCL) was originally identified in the Kiel classification as a "centrocytic lymphoma" [1]. This type of lymphoma was termed a lymphocytic lymphoma of intermediate differentiation by Berard and Dorfman [2]. A distinct subtype of MCL was characterized by atypical small lymphoid cells with wide mantles around benign germinal centers and was called a mantle zone lymphoma [3]. With the advent of the revised European-American and the later World Health Organization classifications, MCL was made a distinct lymphoma subtype and was termed an aggressive lymphoma [4,5]. MCL represents about 4% of all lymphomas in the US and 7–9% in Europe [6].

Patients with MCL have a median age in their 60s and have a striking male predominance (2:1). Patients generally have stage III/IV disease and present with extensive lymphadenopathy, blood and bone marrow involvement, and splenomegaly [7]. Eighty percent of the patients with the mantle zone variant have splenomegaly which may be massive. The MCL patients can present with pancytopenia or a leukemic presentation with extensive leukocytosis [8]. Some degree of peripheral blood involvement can be detected in most cases by flow cytometry [9]. Other extranodal sites include the gastrointestinal tract either in the stomach or colon, liver, or in Waldeyer's ring [10]. Some patients have sheets of lymphomatous polyps of the large bowel, lymphomatous polyposis, which sometimes leads to the diagnosis of MCL [11]. If random blind biopsies are done of normal appearing mucosa of the colon in patients who have been diagnosed with MCL in other locations, a large percentage are positive for MCL involvement [11]. Other extranodal sites for MCL involvement include the skin, lacrimal glands, and central nervous system [10].

Diagnosis

The diagnosis is made on a biopsy of a lymph node, tissue, bone marrow, or blood phenotype, which shows the typical morphology of monomorphic small to medium sized lymphoid cells with irregular nuclear contours [5]. Four cytologic variants of MCL are recognized, including the small cell variant, mantle zone variant, diffuse variant, and the blastic variant [12]. Immunophenotyping is commonly used with the MCL cells being CD20+, CD5+, and positive for Cyclin D1, whereas being negative for CD10 and Bcl6 [5]. The hallmark chromosomal translocation t(11:14)(q13;32) identifies MCL and can be shown in most cases

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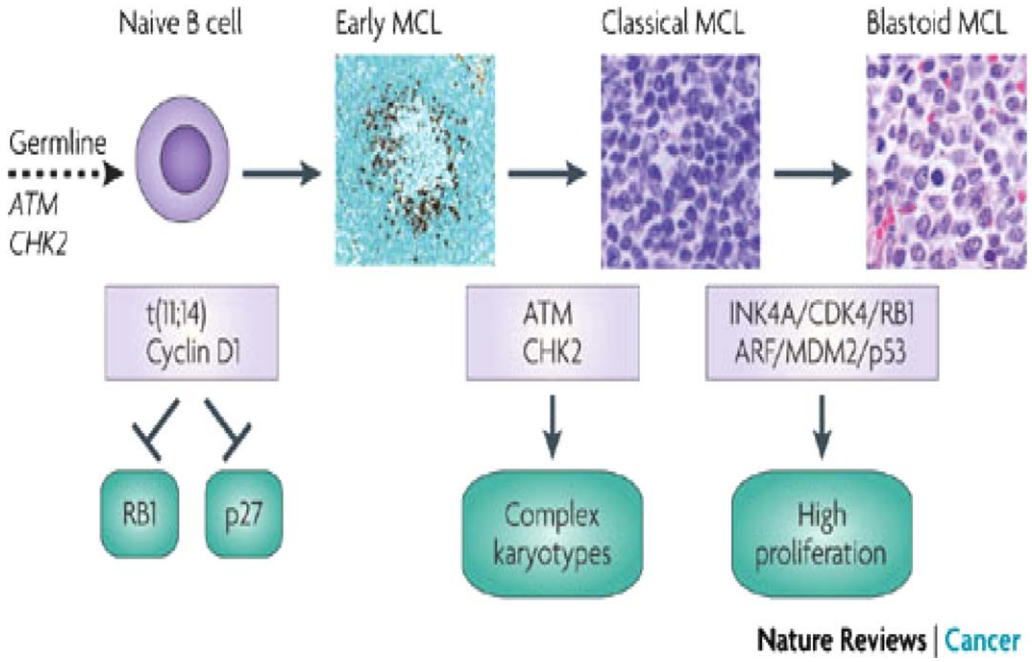

Figure 1. A proposed model of molecular pathogenesis and progression of MCL (Reproduced from Ref. 17, with permission from [Nat Rev Cancer]). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

[13]. This translocation leads to the aberrant expression of cyclin D1, which is not typically expressed in normal lymphocytes. A few cyclin D1 negative cases have been identified and appear to have an overexpression of cyclin D2 or D3 instead [14]. Recently, overexpression of the transcription factor, SOX11, has been described as a diagnostic marker for MCL with the absence of SOX11 a characteristic of indolent MCL [15]. Biologic features such as a high Ki-67 proliferation index or p53 mutations and p16 deletions are closely related to the more aggressive MCL subtypes such as the blastoid variants [16]. A model of molecular pathogenesis and progression of MCL has been proposed by Jares et al. (Fig. 1) [17].

Staging procedures should include a complete blood count, chemistry profile, a lactic dehydrogenase (LDH), a bone marrow evaluation, with immunophenotyping by flow cytometry of the bone marrow and blood, and computed tomography of the chest, abdomen, and pelvis. There are limited studies in using FDG-PET scanning for MCL, but it is often clinically useful. The standard uptake values of sites involved with MCL often have low or intermediate values [18]. Evaluation of the gastrointestinal tract with endoscopy is warranted if there are clinical symptoms or if a dose intense regimen will be used. Evaluation of the cerebral spinal fluid is not usually done unless there are neurologic symptoms or if the patient has the blastoid variant [19]. The majority of patients have stage III or IV disease after complete staging is completed.

Risk Stratification

The International Prognostic Index (IPI) was first developed for patients with diffuse large B-cell non-Hodgkin lymphoma [20]. This was used for patients with MLC but was not very discriminatory, particularly for the lower risk patients. More recently, the first prognostic index for MCL, the Mantle cell International Prognostic Index (MIPI), was formulated by the European MCL Network [21]. The independent prognostic factors for shorter overall survival from the MIPI were higher age, worse ECOG performance

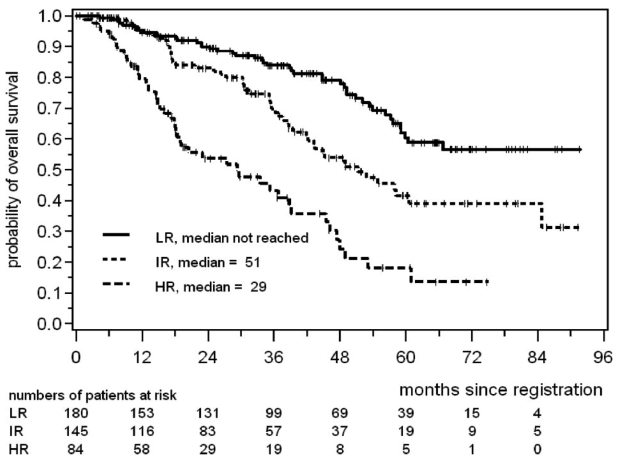

Figure 2. Overall survival for low, intermediate, and high risk MCL according to the MIPI classification (Reproduced from Ref. 21], with permission from [Blood])

status, higher LDH, and a higher white blood cell count at diagnosis. These were calculated as a continuous parameter and three groups emerged: MIPI low-risk with the median overall survival not reached (5-yr OS 60%), MIPI intermediate risk with a median OS of 51 months, and a MIPI high risk group with a median OS of 29 months (Fig. 2)[21]. This index has now been validated by other groups [22] (Table I).

A simplified modification of the MIPI has also been developed, which has high concordance to the original MIPI, but slightly less discriminatory power [21]. The addition of the Ki-67 proliferation index also provides some additional discriminatory power [21] (Table II).

For each prognostic factor, 0 to 3 points are given and the points are summed up to a maximum of 11. Patients with 0–3 points are low risk, patients with 4–5 points are intermediate risk, and patients with 6–11 points are high risk. These risk categories correspond to the categories of the original MIPI [21].

TABLE I. The Original MIPI Score Calculations

[0.0335 × age in (years)] × age (years) + 0.6978 (if ECOG performance status > 1) + 1.367 × $\log_{10}$ (LDH/ULN LDH) + 0.9393 × $\log_{10}$ (white blood cells per 10^6 L)

TABLE II. Simplified MIPI Index

Points	Age, years	ECOG PS	LDH/ULN LDH	WBC, 10^9/L
0	<50	0–1	< 0.67	<6.700
1	50–59	–	0.67–0.99	6.700–9.999
2	60–69	2–4	1.00–1.49	1.0–14.999
3	➢70	–	➢1.500	➢15.000

Gene expression profiling has been performed on a large series of MCL patients to evaluate a molecular predictor consisting of 20 proliferation associated genes [23]. However, a microarray-based technique is not feasible on a wide scale. Therefore, further testing of a minimum number of genes by formalin-fixed, paraffin-embedded tissue specimens has been studied [24]. This study identified five genes including *RAN, MYC, TNFRSF10B, POLE2,* and *SLC29A2* which were validated by a quantitative reverse-transcriptase polymerase chain reaction (qRT-PCR) based test and predicted survival in 73 patients with MCL. Further validation of these genes and technique is needed before this is used outside a research context.

Risk-Adapted Therapy

MCL is responsive to a variety of initial therapies, but relatively short-term remissions are achieved with conventional chemotherapy regimens. The median duration of remission in most trials is 1.5–3 years, and the median OS is 3–6 years with standard chemotherapy. However, there is a wide variation in outcomes with some patients having a very aggressive presentation and succumbing to their disease in a short period of time, while other patients at the opposite end of the spectrum have a very indolent clinical course. Because of the rarity of MCL, most trials have not been large randomized trials, and much of the available information is based on smaller phase II trials with historical controls.

Initial management of asymptomatic low MIPI or elderly MCL patients

Given the unfavorable prognosis and the fact that standard therapy does not appear to cure patients with MCL, a "watch and wait" strategy for patients with asymptomatic, low MIPI or elderly MCL patients should be considered. This strategy would be similar to that used for asymptomatic patients with follicular or other indolent lymphomas. In a study from Weill-Cornell Medical Center, 97 patients with MCL were evaluated [25]. Of the 97, 31 (32%) were observed at the time of initial evaluation. These MCL patients were 46% low-MIPI index when compared to 32% low-MIPI in the patients who received initial treatment. The median time to treatment for the observation group was 12 months (range 4 to 128 months) [25]. When this observational patient group needed treatment, the majority received cyclophosphamide, doxorubicin, oncovin, and prednisone (CHOP)—like treatment (55%), with some patients receiving rituximab monotherapy (13%), and at the time of publication five patients had never received any therapy [25].

When the asymptomatic elderly MCL patient population does become symptomatic and requires therapy, a number of options are available for treatment. Probably, the most commonly used regimen in the past has been an anthracycline-based therapy such as CHOP [26]. Rituximab monotherapy has some modest activity in MCL [27]. More recently, rituximab has been added to the drugs in CHOP (R-CHOP) and tested in MCL. The first report of R-CHOP for the treatment of MCL was in 40 previously untreated patients and yielded an overall response rate (ORR) of 96%, including a complete response (CR) of 48% [28]. Despite 36% of the patients having a molecular CR, there was no difference in the median progression-free survival (PFS) between the patients who achieved a molecular CR (16.5 months) and those who did not (18.8 months) [28]. There were similar results from a randomized study in the German lymphoma study group which compared front-line CHOP to R-CHOP. In this study, the addition of rituximab to CHOP improved the ORR (94% vs. 75%, $P = 0.0054$) and the CR rate (34% vs. 7%, $P = 0.00024$) [29]. However, this did not translate into significant improvements in PFS or OS in this study [29].

Purine analogues have also been used for the treatment of MCL in the older patient population. Single agent fludarabine demonstrated an ORR < 40%; however, when combined with cyclophosphamide and rituximab the response rate is closer to 60% [30,31]. More recently, a large randomized trial done in Germany demonstrated that R-CHOP was superior to R-FC in the older MCL patient population with a 4 year OS of 65% for R-CHOP and 50% for R-FC ($P = 0.0032$) [32]. In addition, a second randomization was done for maintenance either with rituximab or interferon. The arm that produced the best PFS and OS, was R-CHOP followed by rituximab maintenance with a 4-year OS of 87% [32]. This is the first large randomized trial which demonstrated a benefit for rituximab maintenance in PFS for patients with MCL.

Another agent that has been tested in patients with MCL, which demonstrated good activity is Bendamustine. A randomized trial done in Europe compared R-CHOP to R-Bendamustine in a number of different lymphomas [33]. In this trial, the patients with MCL had a similar ORR (89% for BR and 95% for R-CHOP). The BR regimen was associated with a lower progression rate 42% vs. 63% for the R-CHOP arm [33]. In addition, the hematologic toxicity and alopecia were less in the R-Bendamustine arm [33]. A second study evaluating R-CHOP vs. R-Bendamustine did not demonstrate a superior outcome for the R-Bendamustine but did demonstrate an equivalent outcome [34] Some clinical studies are testing agents used in relapsed MCL in combinations in the front-line setting such as R-CHOP + Bortezomib [35].

Recommendations: Asymptomatic elderly or low-MIPI patients can be observed without any therapy. When the patients become symptomatic, first line therapy choices include R-CHOP (± rituximab maintenance), R-Bendamustine, or a clinical trial.

Initial management of a young symptomatic patient

Several studies have suggested that aggressive therapies in younger patients with MCL may improve the outcomes. One of the first studies to evaluate this was the European MCL Network study where responding patients under age 65 years were randomized after induction therapy to receive either myeloablative radio-chemotherapy followed by autologous stem cell transplantation (ASCT) or maintenance interferon [36]. In this study, the patients in the ASCT arm had an improved PFS over those in the interferon arm [36]. Several other single arm and retrospective studies have suggested patients receiving an induction regimen that contains high-dose cytarabine, such as

hyperfractioned cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose cytarabine and methotrexate (HyperCVAD ±rituximab) experience improved survival [37–39].

The addition to rituximab to 6–8 cycles of HyperCVAD alternating with high dose cytarabine and methotrexate yielded a CR rate of 87% and had a 7-year failure-free survival rate of 52% and OS of 68% [37]. This regimen was tested in a multicenter trial and was found to have a similar ORR of 88% and CR rate of 58%; however, there was grade IV hematologic toxicity in 87% of the patients making this regimen difficult to give in some community settings [38]. It was also suggested in a retrospective study that patients receiving R-HyperCVAD as an induction with auto ASCT in CR1 had an improved outcome as compared to R-CHOP [39]. However, a further analysis of a separate cohort of MCL patients demonstrated that when corrected for the MIPI, the outcomes may be similar [40].

Because the R-HyperCVAD alternating with methotrexate/cytarabine is difficult to administer, modifications which drop the methotrexate portion [41] or drop both the methotrexate and cytarabine have been tested [42]. In the study from Geisler et al. [41], 160 younger MCL patients received rituximab + maxi-CHOP, alternating with rituximab + cytarabine. Responders received high-dose chemotherapy with ASCT. The 6-year PFS was 66% and the OS was 70%. Compared to a historical control without the cytarabine, the results were much improved with the regimen as outlined [41]. In a small pilot trial in an older population, the rituximab–Hyper CVAD regimen without the methotrexate or cytarabine, but with maintenance rituximab demonstrated an ORR of 77% and a median PFS of 37 months [42]. Another approach has been for patients to receive R-CHOP X 3 cycles, then Rituximab, cisplatin, cytarabine, dexamethasone (R-DHAP) X 3, followed by high dose chemotherapy and autologous stem cell transplantation [43]. This study also demonstrated an excellent 5-year overall survival of 75% [43].

The role of autologous stem cell transplantation in CR1 has not been tested in a randomized trial. However in a retrospective analysis of 167 MCL patients under age 65, the patients received either R-HyperCVAD or R-CHOP followed by an auto ASCT in CR1 had an improved PFS compared to R-CHOP alone ($P < 0.004$), even when corrected for prognostic factors. [44]. The best induction regimen before transplant has not been defined but is currently being evaluated in clinical trials.

Recommendations: For young symptomatic patients with MCL, considerations include R-HyperCVAD with high-dose cytarabine (±Methotrexate) followed by ASCT in CR1 for selected patients. For patients who are not candidates for standard R-HyperCVAD with high dose cytarabine/methotrexate, possible alternatives include R-CHOP or R-Bendamustine. If possible, ASCT in CR1 should still be considered for these patients as well.

Management of relapse/refractory MCL

For patients with relapsed but asymptomatic MCL, further "watch and wait" maybe possible as there are a percentage of patients with indolent MCL who may not need therapy for months or years. Once the patient becomes symptomatic many options are considerations. The Bendamustine + rituximab (BR) regimen has also been tested in relapsed MCL patients. A phase II study of BR in 63 patients with relapsed/refractory MCL demonstrated an ORR or 90% with a CR of 60% and a median PFS of 30 months [45].

Because many standard lymphoma salvage regimens have limited activity in MCL, novel treatment approaches based on targeting known signaling pathways have been tested. The first such agent to be tested as a proteasome inhibitor, bortezomib. As a monotherapy, bortezomib has demonstrated ORRs in the 30–40% range [46]. In a large phase II study of 141 evaluable MCL patients treated with bortezomib, there was an ORR of 33% with a CR rate of 8% [47]. With further follow up, the phase II study of bortezomib demonstrated a median time to progression of 6.7 months and a median OS of 23.5 months [48]. Bortezomib has also been combined with other agents such as Bendamustine and rituximab in the BVR regimen which also had excellent activity. In patients with MCL, the ORR rate for the BVR regimen was 71% [49].

The PI3Kinase/Akt/mTOR pathway is implicated in the pathogenesis of MCL [50]. Based upon this information the mTOR inhibitor, temsirolimus was tested in a phase II study of patients with relapsed/refractory MCL. In this study, temsirolimus demonstrated moderate activity with an ORR of 44% [51]. In a phase III study of 162 relapsed/refractory patients with MCL, high doses of temsirolimus (175 mg/75 mg) resulted in an ORR of 22% and a PFS of 4.8 months [52]. Other mTOR inhibitors, such as everolimus, have also demonstrated activity in MCL [53].

The immunomodulatory agent lenalidomide has also shown promising activity against MCL. In a phase II study, Zinzani et al. [54] reported an ORR of 41% in 39 MCL patients treated with lenalidomide. The larger EMERGE trial tested single agent lenalidomide in 134 patients with relapsed MCL. The ORR was 28% with a 7.5% CR rate [55]. There studies led to the FDA approval of lenalidomide for patients with relapsed MCL who had failed bortezomib. Lenalidomide has also been combined with rituximab with promising results. In a study by Wang et al. [56], 52 patients with recurrent MCL were treated with lenalidamide and rituximab for recurrent disease. In this study, the ORR was 58% and the CR rate was 33% with the combination being well tolerated.

Other agents that appear to have activity in MCL include the brutons tyrosine kinase (BTK) inhibitor (PCI-32765, Ibruitinib) and PI3Kinase inhibitor (GS-1101, Idelalisib) which target the B-cell receptor pathways. In a study of 51 MCL patients, the BTK inhibitor was reported to have a 69% ORR and a CR rate of 16%, with no differences between bortezomib naïve and patients who had relapsed after receiving bortezomib [57]. Kahl et al. reported on 38 patients with MCL who were treated with Idelalisib who demonstrated a 48% ORR [58].

There is not much data available for standard involved field irradiation in MCL. However, there is data with the use of radioimmunotherapy (RIT) with Yttrium ^{90}—Ibritumomab Tiuxetan in patients with relapsed MCL demonstrating an ORR of 31% [59]. When RIT is used to consolidate after immunochemotherapy, it resulted in improvement of the percentages of responses compared with historical controls [60].

The use of high-dose chemotherapy and ASCT for patients with relapsed MCL has not demonstrated as promising results as with front-line use. However, a resent analysis of the CIBMTR data demonstrated in 159 MCL patients receiving an autologous transplant for relapsed disease, the 5-year OS was 44% and for 99 patients receiving an allogeneic transplant for MCL, the 5-year OS was 32% [61]. In appropriate patients with relapsed MCL who had a long initial remission and have been successfully salvaged, ASCT in CR2 maybe a consideration. Allogeneic stem cell transplantation is felt to be the only potentially curative treatment for advanced MCL. A number of small studies using various reduced intensity preparative regimens with an allogeneic source of stem cell have been reported

[62,63]. In a study by Tam et al. [62], 35 patients with relapsed MCL receiving a reduced intensity regimen with an allogeneic stem cell transplant. With a median follow up of 56 months, the 6-year PFS was 46% and the 6-year actuarial OS was 53% [62]. Although the relapse rates are less with allogeneic transplantation, the risks of graft-versus host disease and infectious complications are much higher resulting in similar short term but apparently improved long term results compared to autologous stem cell transplantation for relapsed MCL.

Recommendations: My first choice for a relapsed MCL patient would be bendamustine/rituximab if the patient has not previously received bendamustine. Other options would include a bortezomib containing regimen or lenalidamide. If the patient is a candidate for stem cell transplantation, consideration for an autologous transplant if there was a long first remission or a reduced intensity allogeneic stem cell transplant should be given. When clinically available, B-cell receptor pathway inhibitors would be an excellent choice for therapy as well.

References

1. Gerard-Marchant R, Hamlin I, Lennert K, et al. Classification of non-Hodgkin's lymphomas [letter]. Lancet 1974;2:405–408.
2. Berard CW, Dorfman RF. Histopathology of malignant lymphomas. Clin Haematol 1974;3:39–45.
3. Weisenburger DD, Kim H, Rappaport H. Mantle-zone lymphoma. A follicular variant of intermediate lymphocytic lymphoma. Cancer 1982;49:1429–1434.
4. Harris NL, Jaffe ES, Stein H, et al. A revised European-American classification of lymphoid neoplasms: A proposal from the International Lymphoma Study Group. Blood 1994;84:1361–1392.
5. Swerdlow SH, Campo E, Harris N, et al. WHO Classification of Tumors of the Haematopietic and Lymphoid Tissues. Lyon, France: IARC; 2008.
6. Non-Hodgkin's Lymphoma Classification project. A clinical evaluation of the International Lymphoma Study Group. Blood 1997;89:3909–3918.
7. Tiemann M, Schrader C, Klapper W, et al. Histopathology, cell proliferation indices and clinical outcome in 304 patients with mantle cell lymphoma (MCL): A clinicopathological study from the European MCL Network. Br J Haematol 2005;131:29–38.
8. Ferrer A, Salaverria I, Bosch F, et al. Leukemic involvement is a common feature in mantle cell lymphoma. Cancer 2007;109:2473–2480.
9. Ghielmini M, Zucca E. How I treat mantle cell lymphoma. Blood 2009;114: 1469–1476.
10. Samaha H, Dumontet C, Ketterer N, et al. Mantle cell lymphoma: A retrospective study of 121 cases. Leukemia 1998;34:329–336.
11. Romaguera JE, Medeiros LJ, Hagemeister FB, et al. Frequency of gastrointestinal involvement and its clinical significance in mantle cell lymphoma. Cancer 2003;97:586–591.
12. Bertoni R, Ponzoni M. The cellular origin of mantle cell lymphoma. Int J Biochem Cell Biol 2007;39:1747–1753.
13. Bertoni F, Rinaldi A, Zucca E, Cavalli F. Update on the molecular biology of mantle cell lymphoma. Hematol Oncol 2006;24:22–27.
14. Rosenwald A, Wright G, Wiestner A, et al. The proliferation gene expression signature is a quantitative integrator of oncogenic events that predicts survival in mantle cell lymphoma. Cancer Cell 2003;3:185–197.
15. Fernandez V, Salamero O, Espinet B, et al. Genomic and gene expression profiling defines indolent forms of mantle cell lymphoma. Cancer Res 2010;70: 1408–1418.
16. Bernard M, Gressin R, Lefrere F, et al. Blastic variant of mantle cell lymphoma: A rare but highly aggressive subtype. Leukemia 2001;15:1785–1791.
17. Jares P, Colomer D, Campo E. Genetic and molecular pathogenesis of mantle cell lymphoma: Perspectives for new targeted therapeutics. Nat Rev Cancer 2007;7:750–762.
18. Gill S, Wolf M, Prince HM, et al. [18F] fluorodeoxyglucose positron emission tomography scanning for staging, response assessment, and disease surveillance in patients with mantle cell lymphoma. Clin Lymphoma Myeloma 2008;8: 159–165.
19. Ferrer A, Bosch F, Villamor N, et al. Central nervous system involvement in mantle cell lymphoma. Ann Onc 2008;19:135–141.
20. International Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for aggressive non-Hodgkin's lymphoma. N Engl J Med 1993;329: 987–994.
21. Hoster E, Dreyling M, Klapper W, et al. A new prognostic index (MIPI) for patients with advanced mantle cell lymphoma. Blood 2008;111:558–565.
22. Geisler CH, Kolstad A, Laurell A, et al. The mantle cell lymphoma International Prognostic Index (MIPI) is superior to the International Prognostic Index (IPI) in predicting survival following intensive first line immunochemotherapy and autologous stem cell transplantation (ASCT). Blood 2010;115:1530–1533.
23. Rosenwald A, Wright G, Wiestner A, et al. The proliferation gene expression signature is a quantitative integrator of oncogenic events that predicts survival in mantle cell lymphoma. Cancer Cell 2003;3:185–197.
24. Hartmann E, Fernandez V, Moreno V, et al. Five-gene model to predict survival in mantle-cell lymphoma using frozen or formalin-fixed, paraffin-embedded tissue. J Clin Onc 2008;26:4966–4972.
25. Martin P, Chadburn A, Christos P, et al. Outcome of deferred initial therapy in mantle-cell lymphoma. J Clin Onc 2009;27:1209–1213.
26. Weisenburger DD, Vose JM, Greiner TC, et al. Mantle cell lymphoma: A clinicopathologic study of 68 cases from the Nebraska Lymphoma Study Group. Am J Hematol 2000;64:190–196.
27. Foran JM, Rohatiner AZ, Cunningham D, et al. European phase II study of rituximab (chimeric anti-CD20 monoclonal antibody) for patients with newly diagnosed mantle-cell lymphoma and previously treated mantle-cell lymphoma, immunocytoma, and small B-cell lymphocytic lymphoma. J Clin Onc 2000;18: 317–324.
28. Howard OM, Gribben JG, Neuberg DS, et al. Rituximab and CHOP induction therapy for newly diagnosed mantle-cell lymphoma: Molecular complete responses are not predictive of progression-free survival. J Clin Onc 2002;20: 1288–1294.
29. Lenz G, Dreyling M, Hoster E, et al. Immunochemotherapy with rituximab and cyclophosphamide, doxorubicin, vincristine, and prednisone significantly improves response and time to treatment failure, but not long term outcome in patients with previously untreated mantle cell lymphoma: Results of a prospective randomized trial of the German Low Grade Lymphoma Study Group (GLSG). J Clin Onc 2005;23:1984–1992.
30. Foran JM, Rohatiner AZ, Coiffier B, et al. Multicenter phase II study of fludarabine phosphate for patients with newly diagnosed lymphplasmacytoid lymphoma, Waldenstrom's macroglobulinemia, and mantle cell lymphoma. J Clin Oncol 1999;17:546–553.
31. Cohen BJ, Moskowitz C, Straus D, et al. Cyclophsphamide/fludarabine (CF) is active in the treatment of mantle cell lymphoma. Leuk Lymphoma 2001;42: 1015–1022.
32. Kluin-Nelemans JC, Hoster E, Hermine O, et al. Treatment of older patients with mantle cell lymphoma. NEJM 2012;376:520–531.
33. Rummel M, Niederle N, Maschmeyer G, et al. Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: An open-label, muticentre, randomised, phase 3 non-inferiority trial. Lancet 2013;381:1203–1210.
34. Flinn IW, Van der Jagt RH, Kahl BS, et al. An open-level, randomized study of bendamustine and rituximab (BR) compared with rituximab, cyclophosphamide, vincristine, and prednisone (R-CVP) or rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) in first-line treatment of patients with advanced indolent non-Hodgkin's lymphoma (NHL) or mantle cell lymphoma (MCL): The Bright Study. Blood 2012;121:902a.
35. Ruan J, Martin P, Furman RR, et al. Bortezomib plus CHOP-Rituximab for previously untreated diffuse large B-cell lymphoma and mantle cell lymphoma. J Clin Onc 2010;29:690–697.
36. Dreyling M, Lenz G, Hoster E, et al. Early consolidation by myeloablative radiochemotherapy followed by autologous stem cell transplantation in first remission significantly prolongs progression-free survival in mantle cell lymphoma: Results of a prospective randomized trial of the European MCL Network. Blood 2005;105:2677–2684.
37. Romaguera JE, Fayad L, Rodriguez MA, et al. High rate of durable remission after treatment of newly diagnosed aggressive mantle-cell lymphoma with rituximab plus HyperCVAD Alternating with Rituximab plus high-dose methotrexate and cytarabine. J Clin Onc 2005;23:7013–7023.
38. Bernstein SH, Epner E, Unger JM, et al. A phase II multicenter trial of HyperCVAD MTX/Ara-C and rituximab in patients with previously untreated mantle cell lymphoma: SWOG 0213. Ann Onc 2013;24:1587–1593.
39. Vose J, Loberiza F, Bierman P, et al. Mantle cell lymphoma (MCL): Induction therapy with HyperCVAD/high dose methotrexate and cytarabine (MC) +/− rituximab improves results of autologous stem cell transplant in first remission. J Clin Onc 2006;24:424a.
40. Budde LE, Guthrie KA, Till GB, et al. Mantel cell lymphoma International Prognostic Index but not pretransplantation induction regimen predicts survival for patients with mantle-cell lymphoma receiving high-dose therapy and autologous stem cell transplantation. J Clin Oncol 2011;29:3023–3029.
41. Giesler CH, Kolstad A, Lurell A, et al. Long-term progression-free survival of mantle cell lymphoma after intensive front-line immunochemotherapy with in vivo-purged stem cell rescue: A non-randomized phase 2 multicenter study by the Nordic Lymphoma Group. Blood 2008;112:2687–2693.
42. Kahl BS, Longo WL, Eickhoff JC, et al. Maintenance rituximab following induction chemoimmunotherapy may prolong progression-free survival in mantle cell lymphoma: A pilot study from the Wisconsin Oncology Network. Ann Oncol 2006;17:1418–1423.
43. Delarue R, Haioun C, Ribrag V, et al. CHOP and DHAP plus rituximab followed by autologous stem cell transplantation in mantle cell lymphoma: A phase 2 study from the Groupe d'Etude des Lymphomes de l'Adulte. Blood 2013;121:48–53.
44. LeCase AS, Vandergrift JL, Rodriguez MA, et al. Comparative outcome of initial therapy for younger patients with mantle cell lymphoma: An analysis form the NCCN NHL Database. Blood 2012;119:093–2099.
45. Rummel M, Atta J, Welslau M. Bendamustine and rituximab (BR) are effective and has a favorable toxicity profile in the treatment of mantle cell and low-grade non-Hodgkin's lymphoma. J Clin Onc 2005;23:3383–3389.

46. O'Connor OA, Wright J, Moskowitz C, et al. Phase II clinical experience with the novel proteasome inhibitor bortezomib in patients with indolent non-Hodgkin's lymphoma and mantle cell lymphoma. J Clin Oncol 2005;23:676–684.
47. Fisher RI, Bernstein SH, Kahl BS, et al. Multicenter phase II study of bortezomib in patients with relapsed or refractory mantle cell lymphoma. J Clin Oncol 2006;24:4867–4874.
48. Goy A, Bernstein SH, Kahl BS, et al. Bortezomib in patients with relapsed or refractory mantle cell lymphoma: Updated time-to-event analyses of the multicenter phase 2 PINNACLE study. Ann Onc 2009;20:520–525.
49. Friedberg JW, Vose JM, Kelly JL, et al. The combination of bendamustine, bortezomib, and rituximab for patients with relapsed/refractory indolent and mantle cell lymphoma. Blood 2011;117:2807–2812.
50. Perez-Galan P, Dreyling M, Wiestner A. Mantle cell lymphoma: Biology, pathogenesis, and the molecular basis of treatment in the genomic era. Blood 2011; 117:26–38.
51. Ansell SM, Inwards DJ, Rowland KM, et al. Low-dose single-agent temsirolimus for relapsed mantle cell lymphoma: A phase 2 trial in the North Central Cancer Treatment Group. Cancer 2008;113:508–514.
52. Hess G, Herbrecht R, Romaguera J, et al. Phase III study to evaluate temsirolimus compared with investigator's choice therapy for the treatment of relapsed or refractory mantle cell lymphoma. J Clin Oncol 2009;27:3822–3829.
53. Witzig TE, Reeder CB, LaPlant BR, et al. A phase II trial of the oral mTOR inhibitor everoliumus in relapsed aggressive lymphoma. Leukemia 2011;25: 341–347.
54. Zinzani PL, Witzig TE, Vose J, et al. Confirmation of the efficacy and safety of lenalidomide oral monotherapy in patients with relapsed or refractory mantle cell lymphoma: Results of an international study (NHL-003). Blood 2008;112:262–267.
55. Goy A, Sinha R, Williams ME, et al. Single-agent lenalidomide in patients with mangle-cell lymphoma who relapsed or progressed after or were refractory to bortezomib: Phase II MCL-001 (EMERGE) Study. J Clin Onc 2013;49:2835.
56. Wang M, Fayad L, Wagner-Bartak N, et al. Lenalidamide in combination with rituximab for patients with relapsed or refractory mantle-cell lymphoma: A phase 1/2 clinical trial. Lancet Oncol 2012;13:716–723.
57. Wang L, Rule S, Martin P, et al. Targeting BTK with Ibruitinib in relapsed or refractory mantle cell lymphoma. NEJM 2013;369:507–516.
58. Kahl B, Byrd J, Flinn I, et al. Significant clinical activity of CAL-101, an isoform selective inhibitor of phosphatidylinositol 3 kinase P110D, in patients with relapsed or refractory indolent and mantle cell lymphoma. Ann Onc 2011;22:350a.
59. Wang M, Oki Y, Pro B, et al. Phase II study of Yttrium-90 Ibritumomab tiuxetan in patients with relapsed or refractory mantle cell lymphoma. J Clin Oncol 2009;27:5213–5218.
60. Smith MR, Linjun A, Gordon LI, et al. Phase II study of rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone immunochemotherapy followed by 90Y-Ibritumomab tiuxetan in untreated mantle cell lymphoma: Eastern Cooperative Oncology Group Study E1499. J Clin Oncol 2012;30:3119–3126.
61. Fenske TS, Carreras J, Zhang M, et al. Outcome of patients with mantle cell lymphoma undergoing autologous versus reduced-intensity allogeneic transplantation. Ann Onc 2011;22:18a.
62. Tam CS, Bassett R, Ledesma C, et al. Mature results of the M. D. Anderson Cancer Center risk-adapted transplantation strategy in mantle cell lymphoma. Blood 2009;113:4144–4152.
63. Maris MB, Sandmaier M, Storer FE, et al. Allogeneic hematopoietic cell transplantation after fludarabine and 2 Gy total body irradiation for relapsed and refractory mantle cell lymphoma. Blood 2004;104:3535–3542.