LEUKEMIA & LYMPHOMA SOCIETY®

Mantle Cell Lymphoma

No. 4 in a series providing the latest information for patients, caregivers and healthcare professionals

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Highlights

- Mantle cell lymphoma (MCL) is one of several subtypes of B-cell non-Hodgkin lymphoma. Most mantle cell lymphomas start from B cells found in the mantle zone within a lymph node.
- MCL usually begins with lymph node enlargement; it can spread to other tissues, such as the bone marrow, liver and the gastrointestinal (GI) tract. Other sites that may be affected include the skin, the lacrimal glands (the glands that produce tears), the lungs and the central nervous system (CNS).
- MCL is distinguished by overexpression of cyclin D1 (a protein that stimulates cell growth) in almost all cases. The overexpression of cyclin D1 is usually caused by a rearrangement (translocation) between chromosomes 11 and 14, or t(11;14).
- A number of chemotherapy plus rituximab (Rituxan®) combinations are used to treat MCL. Rituximab may also be used either alone or in combination with other agents, as a maintenance treatment.
- Four drugs have been approved in recent years to treat relapsed and refractory MCL. These are acalabrutinib (Calquence®), bortezomib (Velcade®), lenalidomide (Revlimid®) and ibrutinib (Imbruvica®).
- Autologous stem cell transplantation may be used to treat MCL patients in their first complete remission. Treatment with allogeneic stem cell transplantation or reduced-intensity allogeneic stem cell transplantation may be beneficial for some patients. This determination is based upon the patient's overall health and the availability of a matched stem cell donor.
- Many clinical trials are under way to study the efficacy and safety of potential new drugs and drug combinations.

Introduction

Lymphoma is the general name for many related subtypes of cancer that arise from a type of white blood cell called a "lymphocyte." Lymphoma is divided into two major categories: Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). Mantle cell lymphoma (MCL) is one of about 70 different subtypes of NHL. Knowing your disease subtype is important because the treatment approach is based on the subtype. For additional free information about NHL subtypes, please see The Leukemia & Lymphoma Society (LLS) booklet *Non-Hodgkin Lymphoma*.

Lymphoma may arise in any one of three types of lymphocytes: B lymphocytes (B cells), T lymphocytes (T cells) and natural killer (NK) cells. B lymphocytes make antibodies to fight infection; T lymphocytes help fight infections and attack cancer cells detected early; and natural killer cells also attack cancer cells and eliminate viruses. B-cell lymphomas are more common than T-cell lymphomas. Most lymphocytes are found in the lymphatic system, which includes the lymph nodes (small bean-shaped structures located in all parts of the body), the spleen and the tonsils.

This booklet includes information about the diagnosis and management of MCL. It also provides specific information on the stages and treatment of the disease, new treatments undergoing investigation and support resources.

About Mantle Cell Lymphoma

Mantle cell lymphoma (MCL) results from a malignant (cancerous) change of a B lymphocyte within a lymph node. Inside a lymph node, there are parts called germinal centers that are formed to respond to a foreign substance, usually a protein, called an "antigen." Antigens create an immune response when eaten, inhaled, or come into contact with the skin or mucous membranes. Inside germinal centers, B lymphocytes make antibodies, which are proteins used by the immune system to neutralize bacteria, viruses, or antigens. Antibodies help the body fight against invaders that make people get sick. Most mantle cell lymphomas start in B lymphocytes that have not passed through a germinal center; instead, they are found in the outer edge of a lymph node follicle called the mantle zone. These transformed

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B lymphocytes (lymphoma cells), which have grown and multiplied in an uncontrolled way, accumulate and cause enlargement of lymph nodes. Sometimes, when these lymph nodes become very large, they may be called "tumors." The MCL cells can enter the lymphatic channels and the bloodstream, then spread to other lymph nodes, tissues or organs, such as the marrow, liver and gastrointestinal tract.

In the United States, about 72,240 new cases of NHL were expected to be diagnosed in 2017. MCL patients represent about 4 percent of all patients with lymphomas and approximately 6 percent of all new cases of NHL in the United States. MCL occurs more frequently in older adults—the average age at diagnosis is the mid-60s. It is more often diagnosed (2:1 ratio) in males than in females.

About 85 percent of patients with MCL have a characteristic genetic lesion that involves chromosome 11 and chromosome 14. This is called a "reciprocal translocation," and is abbreviated as t(11;14). This translocation results when short segments of chromosome 11 and chromosome 14 break off and exchange places. The exchange occurs at the site of the cyclin D1 gene on chromosome 11 and the site of a gene that controls the formation of antibody molecules on chromosome 14. The t(11;14) triggers an overproduction of cyclin D1, a protein that causes tumor cell division and growth. Cyclin D1 is not generally expressed in healthy lymphocytes. The overproduction of the cyclin D1 protein leads to an accumulation of large numbers of MCL cells.

Most MCL patients have the t(11;14) translocation, which leads to the abnormal expression of cyclin D1. However, a few t(11;14) and cyclin D1-negative cases have been identified, and these patients appear to have an overexpression of the proteins cyclin D2 or D3 instead.

The overexpression of the transcription factor SOX11 is observed in nearly all cases of MCL, regardless of the presence of cyclin D1. Overexpression of SOX11 may potentially help in differentiating cyclin D1-negative MCL cases from other types of B-cell lymphomas. It has become a diagnostic marker for MCL and is still being studied.

Signs, Symptoms and Complications

Most patients with MCL have disease involving multiple lymph nodes and other sites of the body. These sites may include the spleen, marrow and blood, the lymph nodes in the throat (tonsils and adenoids), the liver, or the gastrointestinal tract (stomach or colon). Other sites that may be affected include the skin, lacrimal (tear) glands, lungs and the central nervous system.

Patients who have MCL may experience loss of appetite and weight loss; fever; night sweats; nausea and/or vomiting; indigestion, abdominal pain or bloating; a feeling of "fullness" or discomfort as a result of enlarged tonsils, liver or spleen; pressure or pain in the lower back that often extends down one or both legs; or fatigue from anemia.

Commonly seen complications from disease progression may include

- Low blood cell counts, or cytopenias (neutropenia [low white blood cell counts], anemia [low red blood cell counts] and/or thrombocytopenia [low numbers of platelets]). These low counts are caused by the growing lymphoma cells in the bone marrow crowding out normal blood cells and decreasing blood cell production.
- Gastrointestinal, pulmonary, or central nervous system (CNS) complications. Because the MCL is extranodal (occurring in organs outside the lymph nodes), multiple small-intestine polyps may develop in the gastrointestinal tract (GI) as a result of lymphoma cell growth.
- Leukocytosis (a high white blood cell count) may result if the disease grows in the arteries and veins (peripheral blood), producing a leukemia phase of the disease.

Diagnosis

A patient who has a potential diagnosis of lymphoma needs to make sure that his or her subtype has been correctly identified. Treatment depends on knowing the specific subtype. Each patient should be evaluated by a hematologist/oncologist, a doctor who specializes in treating patients who have NHL.

The initial workup for newly diagnosed MCL should include

- Physical examination, with close attention paid to lymph node areas
- Evaluation of patient's performance status (patient's ability to perform certain activities of daily living [ADLs] without the help of others)
- Presence of lymphoma symptoms.

Laboratory assessments should include

- Complete blood count (CBC) with differential and a comprehensive metabolic panel
- Measurement of serum lactate dehydrogenase (LDH)

Lymphomas are diagnosed by the examination of affected tissue, obtained from a surgical biopsy, usually of a lymph node. It is important to be aware that the number of cells obtained from a fine-needle aspiration (FNA) is NOT sufficient to establish a diagnosis. A hematopathologist (a

doctor who specializes in examining tissue and diagnosing disease) will study the proteins on the cells' surface. An immunohistochemistry (IHC) panel is a test used to identify these proteins. It involves applying a chemical marker to the cells and then looking at them under the microscope. Another test called "flow cytometry" may be utilized to assess the surface proteins on lymphoma cells. A diagnosis of MCL is made if the examination of the tissue shows that the lymphoma cells

- Have surface markers of B cells (eg, cluster of differentiation [CD20])
- Overexpress the cyclin D1 protein within the cells
- Contain t(11;14)
- Overexpress the SOX11 transcription factor

Body imaging scans may also be done to determine the extent of disease.

A hematopathologist will determine if the MCL is the common type (found in most patients) or a rare variant. There are four recognized variants of cell shape in MCL, which include the small cell variant, classic variant, pleomorphic variant and the blastic or blastoid variant. In the blastoid variant, the cells are bigger and they grow and divide more rapidly; they are more aggressive and are more challenging to treat. The blastoid variant of MCL may be present at diagnosis or may emerge over time. The pleomorphic variant of MCL is associated with a poorer prognosis (predicting the future course of disease and the chance of survival).

Staging

Staging determines extent of disease, how much the cancer has spread, and where it is located. Staging enables doctors to develop a prognosis and adapt treatment for individual patients to minimize potential toxic effects of therapy.

Tests that are useful in staging of disease include

- Complete blood cell counts (to assess the concentration of red blood cells, white blood cells and platelets) and chemistry profile
- Bone marrow aspiration and biopsy with immunophenotyping by flow cytometry, to determine whether or not the disease has extended beyond the lymph nodes and into the bone marrow
- Imaging studies, including computed tomography (CT) scans of the chest, abdomen and pelvis, or a fluorodeoxyglucose positron emission tomography (FDG-PET) scan, to determine the metabolic activity of the disease. These imaging tests will be used to understand whether the disease is present in the deep lymph nodes, liver, spleen or other parts of the body.
- Studies to check levels of specific proteins in the blood, especially measurements of lactate dehydrogenase (LDH) (a protein found in most cells) and beta2-microglobulin, because these are indirect markers of disease extent and rate of progression. Lactate dehydrogenase is found in the blood when a cell is damaged. A high LDH level may be an indication of cancer or another health problem. When related to cancer, it can indicate that the cancer is widespread.
- Evaluation of the GI tract, which will indicate if there are symptoms associated with this area or if a dose-intensive regimen will be used.
- Evaluation of the cerebral spinal fluid, which is only indicated if the patient has neurological symptoms, a blastoid variant or a high Ki-67. A marker of cell proliferation, Ki-67 shows how fast malignant cells are growing. A high Ki-67 index is associated with poor outcomes in patients with MCL.

When the staging workup is completed, most patients are found to have either stage III or IV disease (see Figure 1 on page 4).

For additional information about laboratory and imaging tests, see the free LLS booklet *Understanding Lab and Imaging Tests*.

Prognostic Factors and Treatment Planning

In order to optimize treatment, doctors determine a prognosis so they can identify patients who may benefit from alternate therapy and those who may need less aggressive therapy. Prognostic indexes help doctors develop treatment strategies based on individual patient risk factors.

The MCL International Prognostic Index (MIPI) is the prognostic system most widely used to help doctors plan treatment. Several clinical factors influence prognosis in MCL. The MIPI score was developed based on four independent factors at the time of diagnosis: age, performance status (ability to perform activities of daily life), lactate dehydrogenase (LDH) levels and leukocyte (white blood cell) count (see Table 1 on page 4). Age and performance status are measures of potential chemotherapy tolerance while LDH and leukocyte count are indirect measures of disease activity.

Simplified MIPI Index

Points (from 0-3/per Prognostic Factor)	Age	ECOG Performance Status	LDH Levels	WBC Count 10^9/L
0	<50	0-1	<0.67	<6.70
1	50-59		0.67-0.99	6.70-9.99
2	60-69	2-4	1.00-1.49	10.00-14.99
3	≥70		≥ 1.50	≥ 15.00

Abbreviations: ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; WBC, white blood cell.

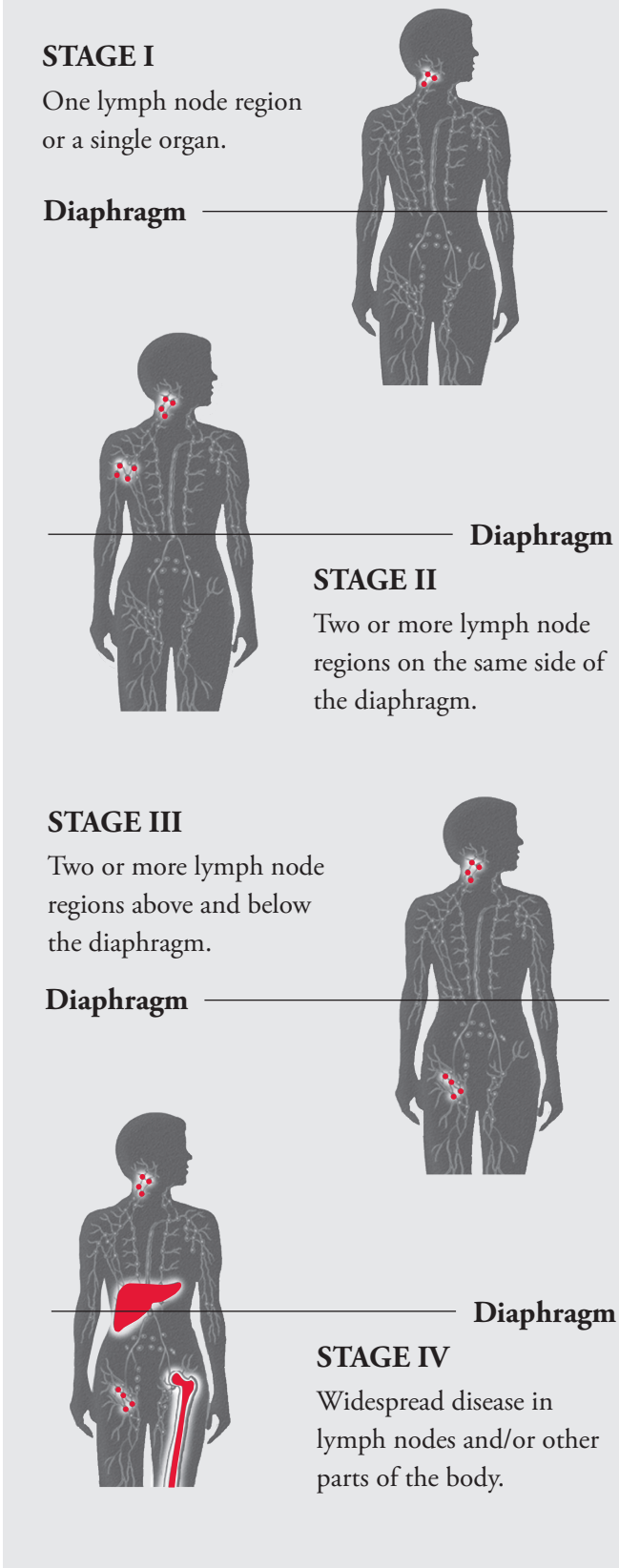
Table 1. The ECOG Scale of Performance Status is a measurement that describes a patient's level of functioning in terms of the ability to care for himself or herself, daily activity, and physical ability. Lactate dehydrogenase is a protein found in most cells. A high LDH level is a sign of cell damage.

For each prognostic factor, 0 to 3 points are given and the points are added up to a maximum of 11. Patients are assigned to a low-risk, intermediate-risk or high-risk category based on the number of points assigned to the number of factors present. Patients with 0 to 3 points are considered to be at low risk, patients with 4 to 5 points at intermediate risk and patients with 6 to 11 points at high risk. A modification of the MIPI also includes the Ki-67 proliferative index, if available.

A number of additional factors have been suggested as potentially important prognostic markers. These include specific gene anomalies as detected by gene expression profiling; minimal residual disease (MRD); MCL cell type; peripheral absolute blood monocyte count (AMC) at diagnosis and beta2-microglobulin level.

Your treatment team may include more than one specialist. It is important for you and members of your team to discuss all treatment options, including new therapies that are being studied in clinical trials. For more information about choosing a doctor or a treatment center, see the free LLS booklet *Choosing a Blood Cancer Specialist or Treatment Center.*

Figure 1. Lymphoma Stages



Treatment

The decision to start treatment will depend on several factors, which include

- The patient's age
- The patient's fitness
- The presence of symptoms
- The patient's MIPI risk category
- Proliferative index
- Cell variant
- Additional—as yet unknown—factors (genetic anomalies)

Treatment for Patients Who Have a Low MIPI Score or Are Asymptomatic Older, Frail MCL Patients. Mantle cell lymphoma is generally considered an aggressive (fast-growing) type of NHL, and most MCL patients receive treatment following diagnosis and staging. However, for a small number of patients who have slow-growing (indolent) MCL and are otherwise well, doctors may recommend a period of close observation, called "watchful waiting."

The doctor will want to schedule visits with these patients every 2 to 3 months, and do imaging tests every 3 to 6 months. The "watch and wait" strategy can also be used in the case of patients who have low MIPI scores and a low proliferation index and nonblastoid/pleomorphic cell shape. For patients with indolent MCL, therapy will begin when symptoms become apparent, when there are signs of disease progression (eg, lymph node enlargement) or when one of the prognostic markers (eg, proliferation index, cell morphology) changes into a poor prognostic marker. Patients who present with symptoms at diagnosis are not appropriate candidates for watchful waiting.

There are a number of options available for treatment. The most commonly used regimen has been the anthracycline-based therapy known as R-CHOP (rituximab [Rituxan®], cyclophosphamide, hydroxydaunomycin [doxorubicin], Oncovin® [vincristine], and prednisone). Rituximab is a monoclonal antibody that targets and destroys cells with the CD20 antigen, including MCL cells. A number of studies show that patients who are treated with chemotherapy plus rituximab have a higher initial response rate than what might be achieved by patients who are treated with chemotherapy alone.

For frail patients, when it is not possible to use aggressive treatments, a number of less intensive therapies are available, including rituximab alone as well as CVP (cyclophosphamide, vincristine and prednisone), chlorambucil, cladribine or thalidomide, usually in combination with rituximab.

Purine analogues such as fludarabine (Fludara®) have also been used for treating elderly MCL patients. Fludarabine demonstrates improved efficacy when combined with cyclophosphamide and rituximab. Single-agent oral chlorambucil (Leukeran®) may be a good choice for frail elderly patients or for patients with serious comorbidities. Less aggressive treatment regimens such as low-dose bendamustine (Bendeka®) in combination with rituximab (B+R) may also be offered, and have recently been shown to be as effective as R-CHOP with less toxicity.

Treatment for Young, Fit Patients. For fit and generally younger patients, the treatment of choice involves a cytarabine-based regimen, which is usually followed by autologous stem cell transplant. Although there is no widely accepted standard, there are several treatment approaches. These include

- R-Hyper-CVAD, which involves the addition of rituximab to 6 to 8 cycles of Hyper-CVAD, alternating with high-dose cytarabine and methotrexate. This intensive and effective regimen may increase response rates, but may also cause more serious side effects. For this reason, it is usually reserved for healthier, often younger patients.

A number of variations of standard R-CHOP chemotherapy have been developed around the world.

- The FDA approved bortezomib (Velcade) to be used in a combination referred to as VcR-CAP (Velcade [bortezomib], rituximab, cyclophosphamide, Adriamycin, [doxorubicin], and prednisone) for previously untreated patients who have MCL.
- The Nordic Lymphoma Group has pioneered a protocol that uses Maxi-R-CHOP (slightly higher CHOP doses) followed by high-dose cytarabine, an agent that many doctors believe is crucial in the treatment of MCL. The chemotherapy is followed by autologous stem cell transplant. This protocol, which has been used in many centers, seems to produce very favorable results.
- Another regimen used is R-DHAP (rituximab, dexamethasone, high-dose Ara-C [cytarabine] and platinum (cisplatin), followed by R-CHOP (in some cases) and consolidated—in both instances—with autologous stem cell transplant.
- More recently, maintenance therapy with rituximab for a number of years has improved the time a patient has without progression, and improved survival.

Treatment for Older, Fit Patients. For older fit patients without significant coexisting illnesses and those who are not eligible for transplantation, the combination of bendamustine (Bendeka®) and rituximab (B+R) may offer an alternative to the standard R-CHOP regimen and should be considered as initial (first-line) treatment in these patients. A study of the bendamustine and rituximab drug combination showed that it is more effective and less toxic than CHOP. See Tables 2 and 3.

Some Drugs Used in MCL Treatment

Chemotherapy

Bendamustine hydrochloride (Bendeka®)
Bortezomib (Velcade®)
Carmustine
Cladribine (Leustatin®)
Cisplatin (Platinol®)
Cytarabine (Ara-C)
Doxorubicin (Adriamycin®, Rubex®)
Etoposide (Etopophos®)
Fludarabine (Fludara®)
Gemcitabine hydrochloride (Gemzar®)
Ifosfamide (Ifex®)
Methotrexate
Pentostatin (Nipent®)
Procarbazine hydrochloride (Matulane®)
Vincristine (Oncovin®)

Immunomodulator

Lenalidomide (Revlimid®)

Steroids

Dexamethasone
Methylprednisolone (Medrol®, Depo-Medrol®, Solu-Medrol®)
Prednisone

Targeted Therapy

Rituximab (Rituxan®)
Ibrutinib (Imbruvica®)
Acalabrutinib (Calquence®)

Table 2. This table lists some of the common drugs used to treat mantle cell lymphoma for both newly diagnosed and previously treated patients.

Chemotherapy Regimens for MCL

Regimen	Features
R-CHOP	• Contains rituximab, cyclophosphamide, hydroxydaunomycin (doxorubicin), Oncovin® (vincristine), and prednisone • Given for up to 6 cycles • Each cycle is 21 days long
R-CHOP/ D-HAP	• 4-cycle regimen; each cycle is 21 days long • Cycles 1 through 4 consist of R-DHAP (rituximab, dexamethasone, high-dose Ara-C [cytarabine], platinum [cisplatin]) • If not in complete remission, then add 4 cycles of R-CHOP (rituximab, cyclophosphamide, hydroxydaunomycin [doxorubicin], Oncovin [vincristine] and prednisone) prior to an autologous stem cell transplantation
VcR-CAP	• 8-cycle regimen; each cycle is 21 days long • Consists of Velcade (bortezomib), rituximab, cyclophosphamide, Adriamycin (doxorubicin) and prednisone
Nordic Lymphoma Group Protocol	• 6-cycle regimen; each cycle is 21 days long • Cycle 1 consists of maxi-CHOP (dose-intensified cyclophosphamide, hydroxydaunomycin [doxorubicin], Oncovin [vincristine] and prednisone) • Cycles 3 and 5 consist of maxi-CHOP with rituximab • Cycles 2 and 4 consist of rituximab and high-dose cytarabine • Cycle 6 consists of high-dose cytarabine with rituximab plus rituximab and stem cell mobilization
R-hyperCVAD	• 8-cycle regimen; each cycle is 21 days long • Cycles 1, 3, 5 and 7 consist of rituximab, cyclophosphamide, vincristine, Adriamycin (doxorubicin) and dexamethasone • Cycles 2, 4 and 6 consist of rituximab, high-dose methotrexate and cytarabine
Modified R-Hyper-CVAD	• Given for up to 6 cycles; each cycle is 28 days long • Given only to people older than 65 y/o • No methotrexate or cytarabine is administered • Rituximab maintenance is received weekly for 4 weeks then repeated every 6 months for 2 years
BR	• Consists of bendamustine and rituximab • Given for up to 6 cycles; each cycle is 28 days long
RCHOP/ RICE	• 6- or 7-cycle regimen; each cycle is 21 days long • First 4 cycles consist of R-CHOP (rituximab, cyclophosphamide, hydroxydaunomycin [doxorubicin], Oncovin [vincristine] and prednisone) • Patients may then receive 2 or 3 cycles of RICE (rituximab, ifosfamide, carboplatin, etoposide)
Cladribine + Rituximab	• Given for up to 6 cycles • Each cycle is 28 days long
CALGB 59909	• Consists of a series of treatments • 2 or 3 cycles of R-M-CHOP (rituximab, methotrexate, cyclophosphamide, hydroxydaunomycin [doxorubicin], Oncovin [vincristine] and prednisone) • 1 cycle of etoposide, cytarabine and rituximab • 1 cycle of high-dose carmustine, etoposide, and cyclophosphamide followed by autologous stem cell transplant • Rituximab maintenance weekly

Table 3. Common chemotherapy combinations for newly diagnosed MCL; may be used with autologous stem cell transplant.

Treatment for Aggressive MCL. For more aggressive forms of MCL, if the disease has spread to the central nervous system (CNS), drugs may be administered directly into the fluid bathing the spinal canal. This procedure is called "intrathecal therapy" (IT). It can also be given preventively in patients at high risk of CNS progression.

Stem Cell Transplantation. Outcomes with conventional chemotherapy have been disappointing. The purpose of autologous stem cell transplantation is to enhance the response to induction therapy and to prolong remission. In autologous stem cell transplantation, a patient's own stem cells are collected, stored (harvested), and frozen. The patient receives intensive high-dose chemotherapy and/or radiation. Then the harvested cells are returned to the patient's own body.

High-dose chemotherapy with autologous stem cell transplantation has resulted in high rates of clinical remission for MCL patients when used during the first complete remission. This may be an option for fit and younger patients who have no symptoms and who have few or no coexisting medical problems. Autologous transplantation combined with effective induction agents, including combinations of monoclonal antibodies and chemotherapy, may offer a longer remission for these patients. Recent research suggests that this procedure, followed by maintenance rituximab, may improve progression-free survival. Some fit older patients may also be candidates for autologous stem cell transplantation. High-dose chemotherapy and autologous stem cell transplantation are less successful when used to treat patients who have relapsed or refractory MCL than when it is used as first-line therapy early in the course of the disease.

Allogeneic stem cell transplantation involves the transfer of stem cells from a donor to the patient following high-dose chemotherapy or radiation therapy. This type of transplant is determined by the patient's overall fitness, medical indications and availability of a suitable donor. There is no specific cut-off age for stem cell transplantation. Allogeneic stem cell transplantation is the only potentially curative option for MCL patients; however, it carries higher risk of serious side effects and complications when compared with autologous transplantation. Reduced-intensity allogeneic transplantation may be an option for older patients. For more information, see the free LLS booklet *Blood and Marrow Stem Cell Transplantation.*

Treatment Side Effects. Side effects will depend on many factors, including the type of treatment and dosage, the age of the patient and coexisting medical conditions. Therapy may cause fever or chills, fatigue, nausea, loss of appetite, mouth sores, peripheral neuropathy (tingling, burning, numbness or pain in the hands or feet), changes in blood cell counts, infection, rash, vomiting, diarrhea, shortness of breath, swelling, temporary loss of hair and other side effects.

Side-effect management is important. If you are having any concerns about potential side effects, talk to the members of your treatment team to get help. Most side effects can be managed without compromising the efficacy of your treatment. In fact, aggressive management of side effects often leads to better treatment outcomes. Most side effects are temporary and resolve when treatment is completed. However, other side effects are long-term and may appear years after the treatment has been completed. Late side effects may include developing another type of cancer, heart disease, low levels of thyroid hormones (hypothyroidism) and loss of fertility.

For additional drug information, see the free LLS booklet *Understanding Side Effects of Drug Therapy* and the Food and Drug Administration (FDA) drug information for consumers Web page at www.fda.gov/drugs/resourcesforyou/consumers/default.htm. Also, see *Treatments Under Investigation* on page 8.

Treatment for Patients with Relapsed or Refractory MCL

Some patients have a return of their disease (a relapse) after achieving remission. Some patients have disease that does not respond to initial treatment (refractory MCL). There is no standard therapy for patients with relapsed or refractory MCL but there are a number of treatment options available.

The following agents have received FDA approval for relapsed and refractory MCL. These include

- Acalabrutinib (Calquence®) is given by mouth and is approved for treatment of adults with MCL who have received at least one prior therapy.
- Bortezomib (Velcade®) is given intravenously (IV) or subcutaneously (injected under the skin), and is approved for patients with relapsed and refractory MCL.
- Ibrutinib (Imbruvica®), a Bruton tyrosine kinase (BTK) inhibitor, is given by mouth and is approved for patients with MCL who have received at least one prior therapy. Ibrutinib has proved to be a very well-tolerated drug with minimal toxicity.
- Lenalidomide (Revlimid®) is an immunomodulatory agent given by mouth, and is approved for patients with MCL whose disease has relapsed or progressed after two prior therapies, one of which included bortezomib.

The addition of rituximab to lenalidomide has achieved better results in patients with relapsed and refractory MCL than when lenalidomide is used as a single agent. This regimen is well tolerated. Bortezomib and/or lenalidomide

combinations may also be effective for patients with refractory MCL. However, depending on how sick the patient is, alternative chemotherapy regimens (eg, bendamustine-, gemcitabine- or fludarabine-based) may be options. In select cases, an allogeneic stem cell transplant may be an alternative.

Several chemoimmunotherapy regimens have been studied in small trials for patients with relapsed and refractory MCL. These include: rituximab, gemcitabine and oxaliplatin; rituximab, fludarabine, cyclophosphamide and mitoxantrone; and bendamustine and rituximab.

Enrollment in clinical trials is always encouraged for patients with relapsed and refractory MCL. If investigational protocols are not available for patients who are candidates for transplant, allogeneic stem cell transplantation has resulted in the best outcomes. For patients who are not candidates for transplant, ibrutinib is considered the most effective single agent.

There are, additionally, several other new drugs under investigation for patients with relapsed and refractory MCL. For more information, please see *Treatments Under Investigation*, below.

Treatments Under Investigation

New approaches under study in clinical trials for MCL treatment, many of which are being supported by LLS research programs, hold the promise of increasing the rate of remission and finding a cure for this disease.

Clinical Trials. Every new drug or treatment regimen goes through a series of studies called "clinical trials" before it becomes part of standard therapy. Clinical trials are carefully designed and reviewed by expert clinicians and researchers to ensure as much safety and scientific accuracy as possible.

Participation in a carefully conducted clinical trial may be the best available therapy. Patient participation in past clinical trials has resulted in the therapies we have today.

LLS Information Specialists, at (800) 955-4572, can offer guidance on how patients can work with their doctors to determine if a specific clinical trial is an appropriate treatment option. Information Specialists will conduct individualized clinical-trial searches for patients, family members and healthcare professionals. When appropriate, personalized clinical-trial navigation by trained nurses is also available.

Research Approaches. There are clinical trials for newly diagnosed patients and for patients with relapsed or refractory disease. A number of approaches are under study in clinical trials for the treatment of patients with MCL.

Some classes of novel therapies and drugs under investigation include

- **PI3K Inhibitors**—These inhibitors are a type of targeted therapy that blocks signals that tell a cell to grow and divide. The phosphoinositide 3-kinase (PI3K) pathway regulates cellular proliferation and survival. The PI3K inhibitor idelalisib (Zydelig®), which has shown encouraging responses in relapsed MCL, is FDA-approved for the treatment of chronic lymphocytic leukemia (CLL) and for the treatment of refractory indolent NHL. This agent, in combination with chemotherapy, monoclonal antibodies and other new drugs, is being explored for the treatment of heavily pretreated MCL patients.
- **mTOR Inhibitors**—These agents work to slow or inhibit MCL by reducing cell expression of cyclin D1 and other important proteins responsible for cancer cell growth. Blocking mTOR activity in MCL leads to antiproliferative effects and, sometimes, to cell death. These drugs have demonstrated activity in MCL, both alone and in combination with other therapies. Examples of mTOR inhibitors under investigation include
  - **Temsirolimus (Torisel®)** for relapsed MCL. Several studies are evaluating temsirolimus as combination therapy with conventional chemotherapy (single agent or combination), immunomodulatory agents (eg, lenalidomide), monoclonal antibodies (eg, rituximab), alkylating agents (eg, bendamustine) and proteasome inhibitors (eg, bortezomib) for untreated and for relapsed or refractory MCL.
  - **Everolimus (Afinitor®)** is a medication that blocks cancer proliferation by cutting off the blood supply to cancer cells. This agent is being studied in patients who have advanced, refractory, or relapsed MCL. This drug is also being studied in combination with other drugs, such as lenalidomide, bortezomib and bendamustine/rituximab, for patients who have relapsed MCL.
- **Cell Cycle Inhibitors.** These drugs interfere with the process of cell division that enables tumors to grow.
  - **Palbociclib (Ibrance®)** is a cyclin-dependent kinase (CDK) 4/6 inhibitor that decreases tumor cell proliferation and sensitizes ibrutinib-resistant MCL cells to PI3K inhibitors. It is being studied in clinical trials as a single agent and in combination with other drugs such as bortezomib and ibrutinib for patients who have relapsed and refractory MCL.

- **Abemaciclib (Verzenio™)** is a CDK4/6 inhibitor that has also shown clinical activity in heavily pretreated MCL and is under study.
- **Flavopiridol (Alvocidib)** is a pan-CDK inhibitor being studied in combination with fludarabine and rituximab for both newly diagnosed and previously treated MCL. Another study in trials combined flavopiridol and bortezomib for the treatment of patients with relapsed MCL, and early data shows that the combination was found to be safe and well tolerated.

- **Immunomodulators**—These drugs regulate the function of the immune system and can slow the rate at which cancer cells grow and multiply. **Lenalidomide (Revlimid®)** is an immunomodulator that was approved for the treatment of patients who have relapsed or refractory MCL. This drug may be given if first-time treatment does not work. It is being studied as monotherapy and in combination with rituximab and/or other agents in patients who have relapsed or refractory MCL.
- **Proteasome Inhibitors**—These drugs affect cell pathways by blocking the activity of enzymes that are needed for cell proliferation and survival. **Bortezomib (Velcade®)**, which may also stop the growth of cancer cells by blocking blood flow to the tumor, is being studied together with rituximab and some chemotherapy combinations in both untreated and refractory MCL. **Carfilzomib (Kyprolis®)**, which is FDA approved for the treatment of patients with multiple myeloma, is in clinical studies as single-agent therapy and as combination therapy for patients who have relapsed or refractory MCL. Carfilzomib works by preventing cancer cells from repairing themselves, which may cause cell death.
- **HDAC Inhibitors**—Agents called "histone deacetylase (HDAC) inhibitors" belong to a class of drugs that cause a chemical reaction in tumor cells, preventing them from dividing. An example is the drug **vorinostat (Zolinza®)**, which has shown promising results in newly diagnosed MCL, especially when used in combination with other agents such as rituximab and cladribine. Another HDAC inhibitor is **abexinostat**, which is under study in clinical trials for previously treated disease.
- **Tyrosine Kinase Inhibitors**—BTK inhibitors block a protein called a "Bruton tyrosine kinase" (BTK), which may prevent malignant B cells from growing. The drug **ibrutinib (Imbruvica®)** is used to treat Waldenström macroglobulinemia and has been approved for previously treated MCL. It is under investigation in many trials for relapsed and refractory MCL in combinations including: ibrutinib and the CDK 4/6 inhibitor palbociclib; ibrutinib and bortezomib; ibrutinib and carfilzomib; and ibrutinib and lenalidomide.
- **B-Cell Lymphoma-2 (BCL-2) Inhibitor—Venetoclax (Venclexta™)** is used to treat patients with previously treated chronic lymphocytic leukemia (CLL). It works by binding to a protein called "B-cell lymphoma 2" (BCL-2), which may be found on some types of leukemia and lymphoma cells. Blocking this protein may help kill cancer cells or may make them more sensitive to other drugs. This agent has shown impressive single-agent activity in relapsed or refractory MCL, causing few toxic side effects apart from an increased risk of tumor lysis syndrome.
- **Monoclonal Antibodies**—These are immunotherapy drugs designed to target specific proteins in cancer cells while minimizing harm to healthy cells. Some work by themselves while others are coupled with chemotherapy drugs, toxins or radioactive substances to target malignant cells. The anti-CD20 antibody **obinutuzumab (Gazyva®)** is under study for heavily pretreated MCL patients, including some patients whose disease is refractory to rituximab. The antibody drug conjugate **polatuzumab vedotin** (a combination of the toxin monomethyl auristatin E with an anti-CD79B monoclonal antibody) has shown promising results in early studies with relapsed and refractory MCL patients.
- **Alkylating Agent and an Antimetabolite**—These drugs damage the DNA in cancer cells, causing them to die. **Bendamustine (Bendeka®)** is FDA-approved to treat chronic lymphocytic leukemia and indolent B-cell NHL that has progressed within 6 months of treatment with other anticancer drugs. It is being studied as a single agent and in combination with rituximab in patients who have relapsed or refractory MCL. It is also being studied in combination with rituximab and lenalidomide as first-line treatment for patients older than age 65.
- **Maintenance Treatment with Rituximab**—Maintenance treatment is given to keep patients in remission and to prevent a relapse. Patients who receive initial treatment with rituximab plus chemotherapy and then receive maintenance rituximab may stay in remission longer than if they do not continue on rituximab treatment. Maintenance therapy with rituximab may also provide extended disease control for patients who are either not physically able to withstand aggressive first-line treatment or who are not eligible for stem cell transplant. It is currently under investigation

- As a single-agent maintenance therapy option following combination chemotherapy, to prolong response duration in patients with recurring or refractory MCL
- In combination with lenalidomide, as a maintenance treatment for older MCL patients

- **Reduced-Intensity Stem Cell Transplantation**—Nonmyeloablative or reduced-intensity allogeneic stem cell transplantation, which uses less intensive conditioning therapy prior to the transplant of donor cells, is being compared with a standard allogeneic transplantation in clinical trials for MCL. Some studies have reported favorable long-term outcomes for patients who have relapsed and refractory MCL.
- **Radioimmunotherapy (RIT)**—This is a type of targeted therapy that combines the cancer- killing ability of radiation therapy with the precise targeting of immunotherapy to deliver lethal doses of radiation directly to cancer cells. In RIT, radioisotope (radioactive molecules) are attached to monoclonal antibodies, which bind to cancer cells. RIT delivers a high dose of radiation directly to cancer cells while minimizing toxic effects to normal tissue. The effectiveness of monoclonal antibodies is enhanced when they are combined with a radioisotope such as **yttrium-90 ibritumomab tiuxetan (Zevalin®)**. Zevalin is under study in multiple trials, either alone and or in combination with other agents, such as bortezomib, for the treatment of newly diagnosed as well as relapsed MCL.
- **CAR T-Cell Therapy**—This type of immunotherapy consists of engineering a patient's own immune cells to first recognize and then attack cancerous tumors. This approach has shown very promising results in patients with blood cancers. The patient's T cells are genetically engineered to produce receptors on their surfaces called "chimeric antigen receptors (CARs)." These receptors recognize and bind to a specific target found on the cancer cells. In an ongoing clinical trial, researchers are studying the role of anti-CD19-CAR T-cell therapy in patients with relapsed or refractory aggressive MCL who have an unfavorable prognosis after exhausting all other treatment options.

Treatment Outcomes

There has been truly remarkable progress in the treatment of MCL over the last decades with a near doubling of overall survival, even though relapses are still common. Most patients respond well to initial chemotherapy (either with or without stem cell transplantation). However, for most patients, the disease eventually progresses or returns. Treatment resistance may develop, which means that a patient may become less responsive to chemotherapy.

The median duration of remission according to most studies is 1.5 to 3 years and the median overall survival is 3 to 6 years with standard chemotherapy. However, for younger patients treated with intensified chemotherapy induction regimens, followed by autologous stem cell transplant, median survival is likely to exceed 10 years. In elderly patients the outcomes are not as favorable but the use of maintenance rituximab after chemotherapy regimens has resulted in improvements in survival.

Advances in the treatment of patients who have relapsed and refractory MCL have been made with the recent approvals of bortezomib, lenalidomide and ibrutinib. These agents are now being incorporated into first-line therapy and should further improve response rates and overall survival for patients.

Researchers continue to look for therapies that will prolong remissions and extend survival in patients with MCL. Outcome data cannot determine how any one person will respond. Talk to your doctor for more information.

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We're Here to Help

LLS is the world's largest voluntary health organization dedicated to funding blood cancer research, education and patient services. LLS has chapters throughout the United States and in Canada. To find the chapter nearest to you, visit our Web site at www.LLS.org/chapterfind or contact

The Leukemia & Lymphoma Society
3 International Drive, Suite 200
Rye Brook, NY 10573
Contact an Information Specialist at (800) 955-4572
Email: infocenter@LLS.org

LLS offers free information and services for patients and families touched by blood cancers. The following entries list various resources available to you. Use this information to learn more, to ask questions, and to make the most of your healthcare team.

Consult with an Information Specialist. Information Specialists are master's level oncology social workers, nurses and health educators. They offer up-to-date disease and treatment information. Language services are available. For more information, please

- Call: (800) 955-4572 (M-F, 9 a.m. to 9 p.m. EST)
- Email: infocenter@LLS.org
- Live chat: www.LLS.org/informationspecialists
- Visit: www.LLS.org/informationspecialists

Free Information Booklets. LLS offers free education and support booklets that can either be read online or ordered. For more information, please visit www.LLS.org/booklets.

Información en Español (LLS information in Spanish). For more information, please visit www.LLS.org/espanol.

Telephone/Web Education Programs. LLS offers free telephone/Web and video education programs for patients, caregivers and healthcare professionals. For more information, please visit www.LLS.org/programs.

LLS Community. The one-stop virtual meeting place for talking with other patients and receiving the latest blood cancer resources and information. Share your experiences with other patients and caregivers and get personalized support from trained LLS staff. To join, visit www.LLS.org/community.

Weekly Online Chats. Moderated online chats can provide support and help cancer patients to reach out and share information. For more information, please visit www.LLS.org/chat.

LLS Chapters. LLS offers community support and services in the United States and Canada including the *Patti Robinson Kaufmann First Connection Program* (a peer-to-peer support program), in-person support groups, and other great resources. For more information about these programs or to contact your chapter, please

- Call: (800) 955-4572
- Visit: www.LLS.org/chapterfind

Clinical Trials (Research Studies). New treatments for patients are ongoing. Patients can learn about clinical trials and how to access them. For more information, please call (800) 955-4572 to speak with our LLS Information Specialist who can help conduct clinical-trial searches. When appropriate, personalized clinical trial navigation by trained nurses is also available.

Advocacy. The LLS Office of Public Policy (OPP) engages volunteers in advocating for policies and laws that encourage the development of new treatments and improve access to quality medical care. For more information, please

- Call: (800) 955-4572
- Visit: www.LLS.org/advocacy

Other Resources

The National Cancer Institute (NCI)

(800) 422-6237
www.cancer.gov

The National Cancer Institute, part of the National Institutes of Health, is a national resource center for information and education about all forms of cancer, including mantle cell lymphoma (MCL). The NCI also provides a clinical-trial search feature, the PDQ® Cancer Clinical Trials Registry, at www.cancer.gov/clinicaltrials, where MCL patients can look for clinical trials for their specific subtype.

The National Comprehensive Cancer Network (NCCN)

www.nccn.org
For current practice guidelines visit www.nccn.org, NCCN Clinical Practice Guidelines in Oncology to see what MCL treatments are being used and are most likely covered by insurance companies.

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