LEUKEMIA & LYMPHOMA SOCIETY®

Mantle Cell Lymphoma

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

Highlights

- Mantle cell lymphoma (MCL) is one of several subtypes of B-cell non-Hodgkin lymphoma (NHL). Most mantle cell lymphomas start from B cells found in the region within a lymph node called the mantle zone.
- 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).
- Mantle cell lymphoma is distinguished by the overexpression of a protein that stimulates cell growth called cyclin D1, in almost all cases. Overexpression of cyclin D1 is usually caused by a rearrangement (translocation) between chromosomes 11 and 14, expressed as t(11;14).
- Several combinations of chemotherapy plus rituximab (Rituxan®) are used to treat MCL. Rituximab may also be used either alone or in combination with other agents as a maintenance treatment.
- Several drugs have been approved in recent years to treat relapsed and refractory MCL. These are bortezomib (Velcade®), lenalidomide (Revlimid®) and the Bruton tyrosine kinase (BTK) inhibitors ibrutinib (Imbruvica®), acalabrutinib (Calquence®) and zanubrutinib (Brukinsa®). In addition, the CAR T-cell therapy brexucabtagene autoleucel (Tecartus®) has also been approved to treat MCL patients who have relapsed.
- Autologous stem cell transplantation may be used to treat younger 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 with relapsed or refractory MCL. This determination is based on 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) or natural killer (NK) cells. B lymphocytes make antibodies to fight infection. T lymphocytes help fight infections and attack cancer cells detected early. 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 mantle cell lymphoma (MCL). It also provides specific information on the stages and treatment of the disease, new treatments undergoing investigation and support resources.

All LLS publications mentioned in this booklet are free and can be viewed, downloaded or ordered online at www.LLS.org/booklets.

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, and 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 B lymphocytes (lymphoma cells), which grow and multiply in an uncontrolled way, accumulate and cause enlargement of lymph nodes. Sometimes, when the affected lymph nodes become very large, the nodes may be called "tumors." 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 77,240 new cases of non-Hodgkin lymphoma (NHL) were expected to be diagnosed in 2020. MCL patients represent about 3 to 8 percent of all new cases of NHL in the United States. MCL occurs more frequently in older adults— the average age at diagnosis is approximately 68 years. It is more often diagnosed in males than in females and whites have a higher incidence compared to other ethnicities.

Most patients with MCL have a characteristic genetic lesion (injury) that involves chromosome 11 and chromosome 14. This is called a "reciprocal translocation," abbreviated as t(11;14). This translocation happens 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. This 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(ll;14) patients who are cyclin D1-negative appear to have an overexpression of the proteins cyclin D2 or D3 instead.

There is often an overexpression of the transcription factor SOX11 (transcription factors are proteins that help turn specific genes "on" or "off" by binding to nearby DNA). Overexpression of SOX11 is observed in nearly all cases of classical MCL, regardless of the presence of cyclin D1. This overexpression may potentially help to differentiate 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.

MCL has been categorized into two major subgroups:

- **Classical MCL** is a common variant that presents with lymph node or other extra-nodal (outside the lymph nodes) site involvement and is associated with an aggressive disease course. Patients who have classic MCL exhibit unmutated *IGHV** gene rearrangement, SOX11 overexpression, and a higher degree of genomic abnormalities (mutations).
- **Leukemic non-nodal MCL** is seen in 10% to 20% of MCL cases. Patients typically have high lymphocyte counts and an enlarged spleen. This subset is typically *IGHV**-mutated, lacks expression of SOX11, and is more genetically stable. In most cases, leukemic non-nodal MCL is associated with an indolent (slow-growing) disease course and a more favorable outcome.

*Normal immunoglobulins (antibodies) are made of two heavy chain proteins and two light chain proteins. The immunoglobulin heavy chain variable *(IGHV)* region genes in B cells give instructions for making the heavy chain component. These genes may or may not be mutated in individuals with MCL.

Signs, Symptoms and Complications

Most patients with MCL (70% to 80%) have symptomatic 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, kidneys and the central nervous system (CNS).

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
- Fatigue from anemia

Commonly seen complications from disease progression may include:

- Low blood cell counts, called "cytopenias." Neutropenia (low white blood cell counts), anemia (low red blood cell counts), and/or thrombocytopenia (low numbers of platelets) are caused by growing lymphoma cells in the bone marrow that are crowding out normal blood cells and decreasing blood cell production.
- Gastrointestinal, pulmonary, or central nervous system (CNS) complications. Because the MCL is extra-nodal (occurring in organs outside the lymph nodes), multiple small-intestine polyps may develop in the gastrointestinal (GI) tract because of lymphoma cell growth. Patients with GI tract involvement may present with rectal bleeding and/or anemia related to blood loss from GI tract.
- Leukocytosis (a high white blood cell count). This may result if the disease grows in the arteries and veins (peripheral blood), producing a leukemia phase of the disease.

Diagnosis

A correct diagnosis means identifying the patient's exact subtype of mantle cell lymphoma. Each patient should be evaluated by a hematologist-oncologist, a doctor who specializes in treating patients with blood cancer.

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, which is a patient's ability to perform certain activities of daily living (ADLs) without the help of others
- Presence of lymphoma symptoms

Laboratory tests should include:

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

Additional testing includes:

Tissue Biopsies. Lymphomas are diagnosed by the examination of tissue that has been affected by lymphoma. This is obtained from a surgical biopsy, usually of a lymph node. Fine-needle aspiration (FNA) is NOT sufficient to establish a diagnosis, as too few cells are obtained.

Protein Tests. A hematopathologist (a doctor who specializes in examining tissue and diagnosing disease) will study the proteins on cells' surfaces to determine what is called the "cluster of differentiation" (CD). MCL cells often have CD5, CD20, CD43, and high levels of cyclin D1. An immunohistochemistry (IHC) panel is a test used to identify these proteins. This test involves applying a chemical marker to the cells and then looking at them under a microscope. A test called "flow cytometry" may be utilized to assess the surface proteins on lymphoma cells.

A diagnosis of MCL is made when 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, such as computed tomography (CT) or positron emission tomography combined with a CT scan (PET/CT), 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 in MCL, which include:

- Small cell variant
- Classic variant
- Pleomorphic variant
- Blastic or blastoid variant

Compared with the small cell and classic variants, the pleomorphic and blastic/blastoid variants are typically more aggressive, more challenging to treat, and are associated with a poor prognosis (likely outcome of a disease). Both pleomorphic and blastic/blastoid variants are associated with a high proliferative rate, meaning they grow and divide more rapidly. The blastoid variant of MCL may be present at diagnosis or may emerge over time.

Staging

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

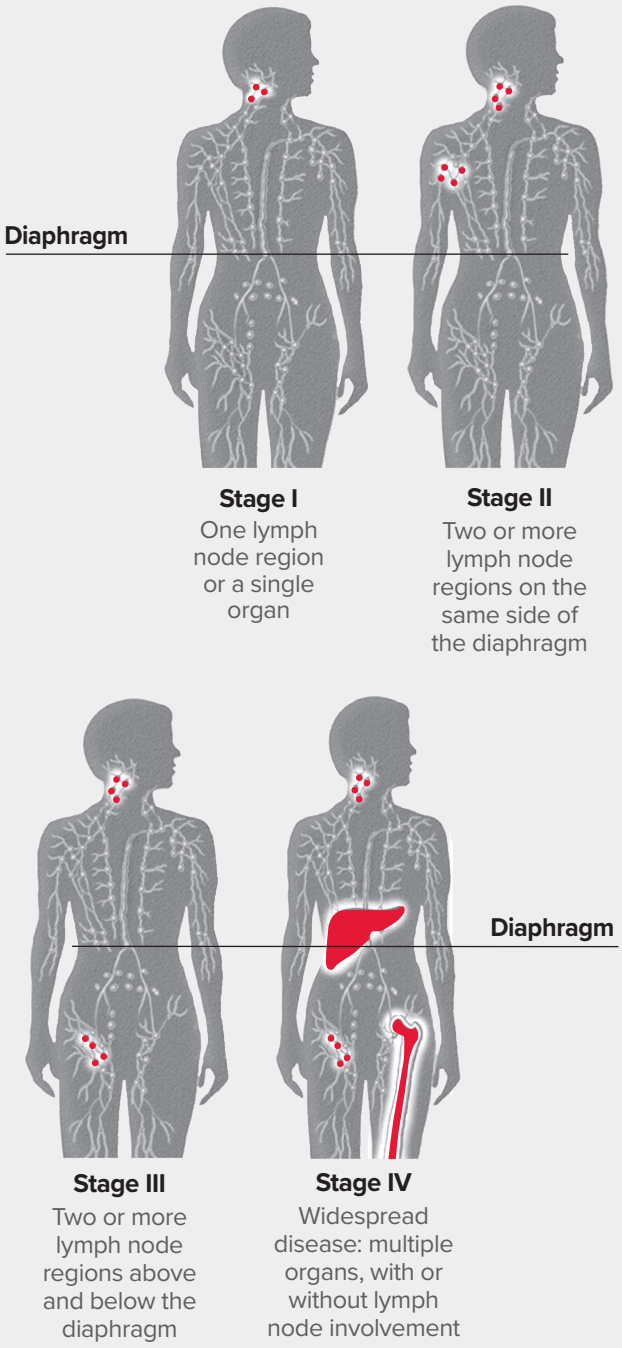
Tests that are useful in staging of disease include:

- Complete blood cell count (CBC) to assess the concentration of red blood cells, white blood cells, and platelets, as well as a chemistry profile
- Bone marrow aspiration and biopsy with immunophenotyping by flow cytometry, to determine whether the disease has extended beyond the lymph nodes and into the bone marrow
- Imaging studies, like x-rays and scans to help doctors see what's going on inside your body. For MCL, these may include 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.
- Lactate dehydrogenase (LDH), a protein found in most cells, and beta-2 microglobulin measurements. These tests check levels of specific proteins in the blood because they are indirect markers of the extent of the disease and its rate of progression. Lactate dehydrogenase (LDH) 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, high LDH can indicate that the cancer is widespread. Beta-2 microglobulin is released by B cells into the blood. High levels can be caused by a fast-growing cancer or other health problems.
- Endoscopy and colonoscopy are procedures that allow doctors to see inside the patient's GI tract. Samples of tissue can be removed during these procedures to be later tested for the presence of cancer cells. GI tract evaluation can help indicate if there are symptoms associated with this area.
- Lumbar puncture evaluates the cerebral spinal fluid. This test is only needed if the patient has neurological symptoms. Involvement of the CNS at the time of the patient's initial visit to the doctor is very rare in MCL.

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

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

Figure 1. Lymphoma Stages



Patients are also divided into "A" or "B" categories. "B" category patients have fever, a lot of sweating and/or weight loss. "A" category patients do not have these symptoms.

All stages of lymphoma can be treated.

Prognostic Factors and Treatment Planning

To optimize treatment, doctors determine a prognosis (likely outcome of a disease) so they can identify patients who may:

- Benefit from alternate therapy
- Need less aggressive therapy

Prognostic indexes help doctors develop treatment strategies based on individual patient risk factors.

One of the most important prognostic markers in MCL is the result of a Ki-67, a test that measures the amount of disease spread called "proliferation." The proliferative index or Ki-67 is a marker of disease spread that shows how fast malignant cells are growing. Evaluation of Ki-67 is performed on tissue obtained from a patient's lymph node biopsy. A high Ki-67 index (>30%) is associated with poor outcomes in patients with MCL.

The most widely used clinical prognostic system is The Simplified MCL International Prognostic Index (MIPI) (See **Table 1,** below). 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
- Leukocyte (white blood cell) count

Age and performance status are measures of potential chemotherapy tolerance, while LDH and leukocyte count are indirect measures of disease activity.

Table 1. Simplified MCL International Prognostic Index (MIPI)

Points	Age	ECOG Performance Status	Lactate Dehydrogenase (LDH) Level	White Blood Cell (WBC) Count 10^9/L
0	<50	0-1	<0.67	<6.70
1	50-59	Not applicable	0.67-0.99	6.70-9.99
2	60-69	2-4	1.00-1.49	10.00-14.99
3	≥70	Not applicable	≥1.50	≥15.00

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

Sources: Dreyling M, Ferrero S. Haematologica. 2016; Vose J. *American Journal of Hematology*. 2017; Mantle Cell Lymphoma Prognostic Index (MIPI) Score. (See References on page 11.)

For each prognostic factor, 0 to 3 points are given and the points are added up to a maximum of 11. Patients are designated into a low-risk, intermediate-risk or high-risk category, based on the number of points assigned to each factor present.

Points	Risk Category
0 to 3 points	Low risk
4 to 5 points	Intermediate risk
6 to 11 points	High risk

There are two modifications of the MIPI: the MIPI-c (MIPI combined) and MIPI-b (biologic MIPI); both also include the Ki-67 proliferative index, if available.

Another important prognostic marker in MCL involves DNA sequencing to identify mutations, or abnormalities, in genes. One gene that can be mutated in MCL is the *TP53* gene. The p53 protein, made by the *TP53* gene, normally acts as the body's master regulator of the DNA repair system and supervises the repair of damaged DNA. *TP53* mutations have been associated with an inferior prognosis in MCL and patients usually have a poor response to standard chemotherapy. *TP53* mutations are more commonly found in patients with high proliferative rates and blastic/blastoid, or pleomorphic variants of MCL.

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 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*.**

Treatment

The decision to start treatment will depend on several factors, including:

- The patient's age
- The patient's fitness
- The presence of symptoms
- The patient's MIPI risk category
- Ki-67 proliferative index
- Cell variant
- MCL group (nodal vs leukemic non-nodal)
- Additional, as yet unknown, factors (such as genetic anomalies)

Mantle Cell Lymphoma

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 healthy, doctors may recommend a period of close observation, called "watchful waiting" or "watch and wait."

Treatment for Patients Who Are Asymptomatic. Asymptomatic means "showing no symptoms." The doctor will schedule visits 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 no symptoms, leukemic non-nodal MCL, normal LDH levels, low MIPI scores, a low Ki-67 proliferation index, or nonblastoid/pleomorphic cell shape. For patients with indolent MCL, therapy will begin when symptoms become apparent, or when there are signs of disease progression (eg, lymph node enlargement). Patients who have symptoms at diagnosis are not appropriate candidates for watch and wait.

For more information about this topic, see the free LLS booklet *Watch and Wait*.

Treatment for Older MCL Patients. This group of patients has several options available for treatment. The most commonly used regimen in the United States is a combination of bendamustine (Bendeka®) and rituximab (BR). Treatment options in older patients also include an anthracycline-based therapy known as R-CHOP (rituximab [Rituxan®], cyclophosphamide, hydroxydaunomycin [doxorubicin], Oncovin® [vincristine], and prednisone) followed by rituximab maintenance. Rituximab is a monoclonal antibody that targets and destroys cells that have the CD20 antigen, including MCL cells. Several studies show that patients who are treated with chemotherapy plus rituximab (chemo-immunotherapy) have a higher initial response rate than patients who are treated with chemotherapy alone. BR has been shown to be as effective, if not more effective, than R-CHOP, with less toxicity.

Treatment options for older MCL patients can include:

- BR—bendamustine (Bendeka®) and rituximab (Rituxan®)
- R-CHOP— (see R-CHOP above)
- VR-CAP—Velcade® (bortezomib), rituximab, cyclophosphamide, Adriamycin® (doxorubicin), and prednisone
- R-squared or R^2—lenalidomide (Revlimid®) and rituximab

Maintenance. Patients who have had less aggressive therapy may benefit from rituximab every 8 weeks until progression or intolerance. Talk to your doctor to see if maintenance is a treatment option for you.

The doctor may decide among these different options depending on age, performance status, existing comorbidities, proliferative index, or other biologic features of MCL.

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

- R-Hyper-CVAD—This treatment is rituximab (Rituxan®) plus 6 to 8 cycles of Hyper-CVAD (cyclophosphamide, vincristine, Adriamycin® [doxorubicin], and dexamethasone), alternating with a combination of high-dose methotrexate and cytarabine. 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, younger patients.
- The Nordic Regimen, pioneered by the Nordic Lymphoma Group, is a protocol that uses Maxi-R-CHOP (slightly higher doses of CHOP and rituximab) alternating with rituximab and high-dose cytarabine. Cytarabine is an agent that many doctors believe is crucial in the treatment of MCL. This chemo-immunotherapy regimen is followed by autologous stem cell transplant. This protocol, which has been used in many centers, seems to produce very favorable results.
- R-DHAP—rituximab, dexamethasone, high-dose Ara-C® (cytarabine), and platinum (carboplatin and cisplatin or oxaliplatin)
- Alternating R-CHOP and R-DHAP
- BR—bendamustine (Bendeka®) and rituximab followed by rituximab and high-dose cytarabine

These protocols are generally consolidated with autologous stem cell transplantation and followed by maintenance therapy. Maintenance therapy with rituximab for a number of years has improved the length of time a patient has no progression and also has improved survival.

Patients with *TP53* and some other mutations have poor outcomes with intensive chemo-immunotherapy consolidated with autologous stem cell transplantation.

For this group of patients, there is no established optimal treatment program. Enrollment in clinical trials is always encouraged for this high-risk subset of patients.

Treatment for Aggressive 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 as a prevention in patients at high risk of CNS progression.

Stem Cell Transplantation. Transplant options for MCL patients include two types: autologous and allogeneic.

The purpose of autologous stem cell transplantation is to enhance the response to induction (first) 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 co-existing 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 not responded to treatment (those with refractory CML), or who have relapsed after transplant is used as first-line therapy.

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 a potentially curative option for MCL patients; however, it carries a higher risk of serious side effects and complications compared with autologous transplantation. Reduced-intensity allogeneic transplantation may be an option for older patients. **For more information, see the free LLS book *Blood and Marrow Stem Cell Transplantation*.**

Treatment for Patients with Relapsed or Refractory MCL

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

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

- Acalabrutinib (Calquence®), a Bruton tyrosine kinase (BTK) inhibitor given by mouth, is approved for adult patients with MCL who have received at least one prior therapy.
- Ibrutinib (Imbruvica®), a Bruton tyrosine kinase inhibitor (BTK) given by mouth, is approved for the treatment of adult patients with MCL who have received at least one prior therapy. According to the NCCN guidelines, ibrutinib can be used in combination with rituximab.
- Zanubrutinib (Brukinsa®), a Bruton tyrosine kinase (BTK) inhibitor given by mouth, is approved for the treatment of adult patients with MCL who have received at least one prior therapy.
- Lenalidomide (Revlimid®), given by mouth, is approved for adult patients with MCL whose disease has relapsed or progressed after two prior therapies, one of which included bortezomib. Lenalidomide can be used in combination with rituximab.
- Bortezomib (Velcade®), given intravenously (IV) or subcutaneously (SC, injected under the skin), is approved for adult patients with MCL.
- Brexucabtagene autoleucel (Tecartus®), a chimeric antigen receptor (CAR) T-cell therapy given by IV, is approved for the treatment of adult patients with relapsed or refractory MCL. This new therapy was granted FDA accelerated approval based on overall response rate and durability of response. Continued approval for this indication may be contingent on verification and description of clinical benefit in a confirmatory trial. Tecartus targets CD19, a protein present in malignant B cells. Tecartus is made by extracting T cells from the MCL patient and genetically modifying those cells to recognize and attack the cancer. After this modification, the cells are infused back into the patient.

The addition of rituximab to lenalidomide has achieved better results in patients with relapsed and refractory MCL than lenalidomide alone. 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 also be options. In select cases, an allogeneic stem cell transplant may be an alternative.

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

Another combination is the oral BCL-2 inhibitor venetoclax (Venclexta®) being studied in combination with the BTK inhibitor ibrutinib.

Enrollment in clinical trials is always encouraged for patients with relapsed and refractory MCL. If treatments in clinical trials are not available and patients are candidates for transplant, allogeneic stem cell transplantation has resulted in the best outcomes.

Additionally, there are several other new drugs under investigation for patients with relapsed and refractory MCL. For more information, please see *Clinical Trials for Blood Cancers* on this page..

Treatment Side Effects

Side effects depend on many factors, including the type of treatment and dosage, the age of the patient and co-existing 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.

Some specialized treatments like chimeric antigen receptor (CAR) T-cell therapy can cause serious and potentially life-threatening side effects. It is important that patients receive this type of therapy from hematology-oncology professionals who have experience in the administration of CAR T-cell therapy and who also know how to prevent and/or manage potential side effects.

Side-effect management is important. If you have 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 effectiveness 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.

Vaccines. Patients with NHL are advised to receive certain vaccinations, including vaccinations for pneumococcal pneumonia and influenza, once they have finished their treatment. There are two types of pneumococcal vaccines available for adults: a pneumococcal polysaccharide vaccine (PPSV23) and a pneumococcal conjugate vaccine (PCV13). Patients with NHL should not be given vaccines that use live organisms or those with high viral loads, such as the herpes zoster (shingles) vaccine, but they can receive Shingrix® because it is an inactivated shingles vaccine. Current COVID-19 vaccines are also recommended, although they have not been specifically tested in patients with MCL as of this printing. Speak to your doctor for more information.

For additional drug information, see the free Side Effect Management series at www.LLS.org/booklets and under All Categories filter for "Side Effect Management." Also see the Food and Drug Administration (FDA) information for consumers Web page at www.fda.gov/drugs/resourcesforyou/consumers/default.htm. Also, see *Treatments Under Investigation* below.

Clinical Trials for Blood Cancers

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 as well as patient advocates to ensure safety and scientific accuracy. Participation in a carefully conducted clinical trial may be the best available treatment option and should be considered each time treatment is discussed with the doctor. Patient participation in past clinical trials has resulted in the therapies we have today. Patients interested in participating in a clinical trial for mantle cell lymphoma (MCL) are encouraged to talk with their hematologist-oncologists about whether a clinical trial would be appropriate for them.

When you and your hematologist-oncologist discuss a clinical trial as a potential treatment option, it may be helpful to:

- Have a list of questions to ask concerning the risks versus the benefits of such a trial (visit www.LLS.org/WhatToAsk for lists of suggested questions).
- Ask a family member, friend, or another advocate accompany you to your doctor visit—both for support and to take notes.

LLS Information Specialists, available at (800) 955-4572, offer guidance on how patients can work with their doctors to determine if a specific clinical trial is an appropriate treatment option. LLS offers help for patients and caregivers in understanding, identifying and accessing clinical trials.

Patients and caregivers can work with Clinical Trial Nurse Navigators who will help find clinical trials and personally assist them throughout the entire clinical trial process. **Visit www.LLS.org/CTSC for more information. Also, visit www.LLS.org/booklets to view *Understanding Clinical Trials for Blood Cancers*.**

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, in 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 allogeneic 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 approvals of bortezomib, lenalidomide, ibrutinib, acalabrutinib, zanubrutinib and the CAR T-cell therapy brexucabtagene autoleucel. These agents are now being evaluated in current clinical trials with the goal to eventually incorporate them into first-line therapy. Researchers expect that incorporating these novel therapies will further improve response rates, overall survival and quality of life for patients. Researchers continue to look for therapies that will prolong remissions and extend survival in patients with MCL.

Keep in mind that the most recent survival statistics for MCL may underestimate actual survival time, because these data do not incorporate outcomes of current treatment options. It is also important to know that outcome data can show how groups of people with MCL responded to treatment, but it cannot determine how any one person will respond. For these reasons, patients are advised to discuss survival information with their doctors.

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Questions to Ask Your Doctor

It may be helpful to prepare some questions to ask your treatment team at your next appointment. Here are some suggestions of questions to ask.

About the Disease and Testing

1. What tests do I need to have?
2. How do I prepare for these tests?
3. Will my medical insurance pay for the tests?
4. When will I have the results? Who will explain the results?
5. What kind of symptoms will I experience?

About Treatment Options and Side Effects

1. Do I need treatment for mantle cell lymphoma?
2. Is the “watch-and-wait” approach the right option for me?
3. What treatment options do I have?

4. Are there any available clinical trials for my diagnosis?
5. Does this hospital/center offer treatment for my disease?
6. How long will the treatment last?
7. What are the side effects of this treatment? How long will they last?
8. How will I know if the treatment is effective? What will happen if the treatment does not work?
9. After initial treatment ends, how will I be monitored? How often will I need to see my treatment team? What type of tests will be required?
10. Are there any long-term side effects of this treatment?

About Cost

1. Will my medical insurance pay for my treatment?
2. If I participate in a clinical trial, am I responsible for any of the costs associated with that clinical trial?
3. What additional costs should I be thinking about (for example, transportation, parking, food)?

Please visit www.LLS.org/WhatToAsk to view question guides on various topics related to coping with blood cancer and its treatment.

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 website 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 highly trained oncology social workers, nurses and health educators. They offer up-to-date disease, treatment and support information. Language services (interpreting and translation) are available. Please contact our Information Specialists or visit our website for more information:

- Call: (800) 955-4572 (Monday through Friday, from 9 am to 9 pm ET)
- Email and Live chat: www.LLS.org/InformationSpecialists

Clinical Trials Support Center (CTSC). Research is ongoing to develop new treatment options for patients. LLS offers help for patients and caregivers in understanding, identifying and accessing clinical trials. Patients and caregivers can work with Clinical Trial Nurse Navigators who will help find clinical trials and personally assist them throughout the entire clinical trial process. Visit www.LLS.org/CTSC for more information.

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

LLS Health Manager™ App. This free mobile app helps you manage your health by tracking side effects, medication, food and hydration, questions for your doctor, and more. Export the information you've tracked in a calendar format and share it with your doctor. You can also set up reminders to take medications, hydrate, and eat. Visit www.LLS.org/HealthManager to download for free.

LLS Coloring for Kids™. This free coloring app allows children (and adults) to express their creativity and offers activities to help them learn about blood cancer and its treatment. The app includes blank canvases, general coloring pages, and pages from LLS coloring books. This app can be used anywhere and may help pass the time in waiting rooms or during treatment. Visit www.LLS.org/ColoringApp to learn more and download.

Financial Assistance. LLS offers financial support including insurance premium and medication co-pay assistance, as well as travel and other needs, to eligible individuals with blood cancer. For more information, please:

- Call: (877) 557-2672
- Visit: www.LLS.org/finances

Información en Español (LLS information in Spanish). Please visit www.LLS.org/espanol for more information.

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

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. Visit www.LLS.org/community to join.

One-on-One Nutrition Consultations. Access free one-on-one nutrition consultations provided by a registered dietitian who has experience in oncology nutrition. Dietitians assist callers with information about healthy eating strategies, side effect management and survivorship nutrition. They also provide additional nutrition resources. Please visit www.LLS.org/nutrition to schedule a consultation or for more information.

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

Podcast. *The Bloodline* with LLS is here to remind you that after a diagnosis comes hope. Listen in as patients, caregivers, advocates, doctors and other healthcare professionals discuss diagnosis, treatment options, quality-of-life concerns, treatment side effects, doctor-patient communication and other important survivorship topics. Visit www.LLS.org/TheBloodline for more information and to subscribe.

LLS Chapters. LLS offers support and services in the United States and Canada including the *Patti Robinson Kaufmann First Connection®* Program (a peer-to-peer support program), local 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

Other Helpful Organizations. LLS offers an extensive list of resources for patients and families. There are resources that provide help with financial assistance, counseling, transportation, patient care and other needs. Please visit www.LLS.org/ResourceDirectory for more information.

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

Information for Veterans. Veterans who were exposed to Agent Orange while serving in Vietnam may be able to get help from the United States Department of Veterans Affairs. For more information please:

- Call: the VA at (800) 749-8387
- Visit: www.publichealth.va.gov/exposures/AgentOrange

World Trade Center (WTC) Survivors. People involved in the aftermath of the 9/11 attacks and subsequently diagnosed with a blood cancer may be eligible for help from the World Trade Center (WTC) Health Program. People eligible for help include:

- Responders
- Workers and volunteers who helped with rescue, recovery and cleanup at the WTC-related sites in New York City (NYC)
- Survivors who were in the NYC disaster area, lived, worked or were in school in the area
- Responders to the Pentagon and the Shanksville, PA, crashes

For more information, please:

- Call: WTC Health Program at (888) 982-4748
- Visit: www.cdc.gov/wtc/faq.html

People Suffering from Depression. Treating depression has benefits for cancer patients. Seek medical advice if your mood does not improve over time—for example, if you feel depressed every day for a 2-week period. For more information, please:

- Call: The National Institute of Mental Health (NIMH) at (866) 615-6464
- Visit: NIMH at www.nimh.nih.gov and enter "depression" in the search box

Other Resources

The National Cancer Institute (NCI)
(800) 422-6237
www.cancer.gov
The National Cancer Institute (NCI), part of the National Institutes of Health (NIH), 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 for Patients* to see what MCL treatments are being used and are most likely covered by insurance companies.

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