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Mantle Cell Lymphoma Facts

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.
- MCL usually begins with lymph node enlargement; it can spread to other tissues such as the bone marrow and liver.
- MCL can involve the gastrointestinal tract.
- 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.
- A number of chemotherapy plus rituximab (Rituxan®) combinations are used to treat MCL.
- Bortezomib (Velcade®) may be used to treat patients who have relapsed disease and has been approved for untreated patients in a combination therapy.
- Ibrutinib (Imbruvica®), a Bruton tyrosine kinase (BTK) inhibitor, is approved for patients with relapsed MCL.
- Autologous stem cell transplantation may be used to treat MCL in first complete remission. Treatment with allogeneic stem cell transplantation or reduced-intensity allogeneic stem cell transplantation may be beneficial for some patients, based upon the availability of a matched related stem cell donor.
- Many clinical trials are under way to study potential improvements in current treatment approaches.

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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.

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 which 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 lymph nodes (small bean-shaped structures located in all parts of the body), the spleen and tonsils, for example.

This publication 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.

For additional free information about NHL subtypes, please see The Leukemia & Lymphoma Society (LLS) publications *Non-Hodgkin Lymphoma* and *The Lymphoma Guide: Information for Patients and Caregivers*.

About Mantle Cell Lymphoma

Mantle cell lymphoma (MCL) results from a malignant transformation of a B lymphocyte in the outer edge of a lymph node follicle (the mantle zone). The transformed B lymphocyte grows in an uncontrolled way, resulting in the accumulation of lymphoma cells, which causes enlargement of lymph nodes. Sometimes, when these lymph nodes become very large, or grow in other parts of the body, they can be called "tumors." The MCL cells can enter the lymphatic channels and the blood, and can spread to other lymph nodes or tissues, such as the marrow, liver and gastrointestinal tract.

In the United States, there are about 70,800 new cases of NHL expected in 2014. MCL patients represent only about 6 percent (about 4,200 cases) 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 in males than in females and white men and women are at a higher risk than black men and women for an MCL diagnosis.

Causes

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 in short segments of chromosome 11 and chromosome 14 exchanging 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. The overproduction of the cyclin D1 protein leads to accumulation of large numbers of MCL cells. This translocation can be thought of as a driver in the behavior of the disease, which likely complements other genetic defects leading to MCL development.

In a small proportion of patients t(11;14) is not present. In most of these patients, other genetic changes cause excess production of cyclin D1. Rarely, MCL arises from overexpression of other cyclin genes (e.g., cyclin D2 and cyclin D3).

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. MCL cells may enter the brain, lungs and spinal cord, although this is relatively rare.

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 developing 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]) since the growing lymphoma cells in the bone marrow crowd out normal blood cells, decreasing blood cell production.
- Gastrointestinal, pulmonary, or central nervous system (CNS) complications because the MCL is extranodal (occurring outside the lymph nodes and in organs). "Multiple small-intestine polyps" may develop in the gastrointestinal tract as a result of the lymphoma cell growth.
- Leukocytosis (high white blood cell counts) may result if the disease grows in the peripheral blood, that is, in the arteries and veins, 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.

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) are NOT sufficient to establish a diagnosis.

Microscopic examination of tissue from the lymph node biopsy can determine if lymphoma is present. A diagnosis of MCL is made if additional examination of the tissue shows that the lymphoma cells

- Have surface markers of B cells (e.g., CD20)
- Overexpress the cyclin D1 protein within the cells
- Contain the translocation 11;14.

Blood tests and body imaging scans may also be done to determine the extent of disease.

A hematopathologist (doctor who specializes in examining tissue and diagnosing disease) will determine if the MCL is the common type (found in most patients) or a rare blastoid variant. In the blastoid variant, the cells are bigger and they grow and divide more rapidly, are more aggressive and are more challenging to treat. The blastoid variant of MCL may be present at diagnosis or may emerge over time.

Staging

Staging determines extent of disease, or how much the cancer has spread, and where it is located. Staging enables doctors to develop a prognosis (predicting the future course of disease and the chance of survival) and tailor treatment to individual patients and 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
- Bone marrow aspiration and biopsy, 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, with or without an accompanying positron emission tomography (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 in other parts of the body (see Figure 1.)
- Studies to check levels of specific proteins in the blood, especially measurements of lactate dehydrogenase (LDH) and beta$_2$-microglobulin, because these are indirect markers of disease extent and rate of progression.

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

Treatment Planning

In order to optimize treatment, doctors determine prognosis (predicting the course of the disease and the chance of survival) so that 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.

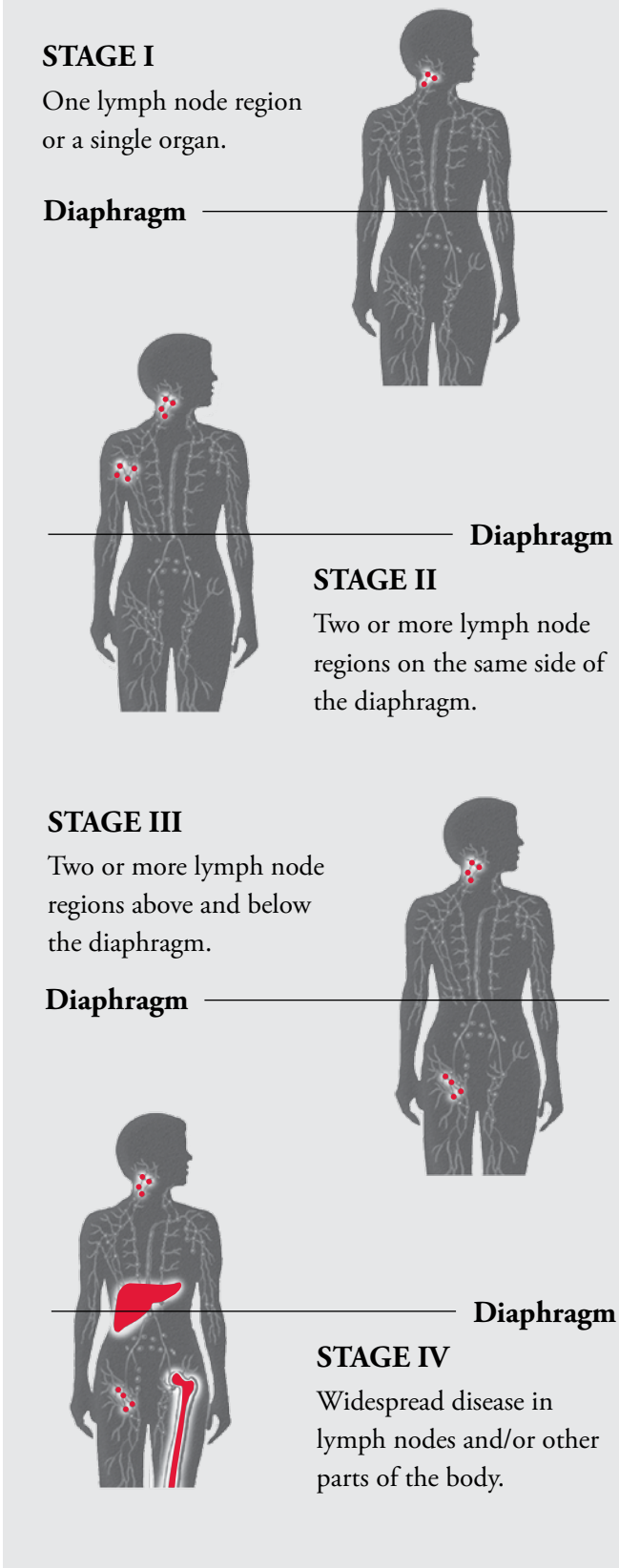
Once the extent of disease has been determined, some doctors who care for MCL patients use The Mantle Cell International Prognostic Index (MIPI) to help plan treatment. Several clinical factors influence prognosis in MCL. The MIPI score was developed based on four independent factors at the time of diagnosis that may correspond with prognosis: age, performance status (ability to perform activities of daily life), lactate dehydrogenase (LDH) levels and leukocyte (white blood cell) count. Age and performance status are measures of chemotherapy tolerance while LDH and leukocyte count are indirect measures of disease activity. 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.

A number of additional factors have been suggested as potentially important prognostic markers, including markers of cell proliferation (Ki-67), which measures how fast malignant cells grow; gene expression profiling; minimal residual disease (MRD); MCL cell type; peripheral blood monocyte count (AMC) at diagnosis and beta$_2$-microglobulin level.

Your treatment team may include more than one specialist. It is important for you and members of your treatment team to discuss all treatment options, including treatments being studied in clinical trials.

For more information about choosing a doctor or a treatment center, see the free LLS publication *Choosing a Blood Cancer Specialist or Treatment Center.*

Figure 1. Lymphoma Stages



Treatment

MCL is generally considered an aggressive (fast-growing) type of B-cell non-Hodgkin lymphoma 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. For patients with indolent MCL, therapy begins when symptoms become more prominent or there are signs of progression (for example, increasing lymph node size, new pain symptoms or new enlarged nodes).

Patients who are having symptoms at diagnosis are not appropriate candidates for watchful waiting, since prompt treatment typically resolves symptoms.

Generally, rituximab (Rituxan®) in combination with other drugs is used to treat patients who have MCL. Rituxan 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 Rituxan have a higher initial response rate than what might be achieved with chemotherapy alone.

In most practices, standard R-CHOP-based chemotherapy is still a commonly used standard of care. While many institutions recommend a protocol that consolidates R-CHOP chemotherapy with a subsequent autologous stem cell transplant, other practices may not endorse this approach.

A number of variations of standard R-CHOP chemotherapy have been developed around the world. Recently, the FDA approved bortezomib (Velcade®) in a combination referred to as VcR-CAP [bortezomib (Velcade), Rituxan, cyclophosphamide, doxorubicin (Adriamycin®) and prednisone] for previously untreated patients with MCL. The Nordic Lymphoma Study Group has pioneered a protocol—appropriate for fit patients–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.

Other centers may recommend R-hyperCVAD, a more intensive chemotherapy. It is an effective regimen and may increase response rates, but these treatments can be very toxic, so, typically, they are reserved for healthier, often younger, patients. Younger patients, however, may want to opt for a less intensive approach.

For older fit patients without significant coexisting illnesses and those who are not eligible for transplantation, the combination of bendamustine (Treanda®) and Rituxan (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 Treanda and Rituxan drug combination showed that it is more effective and less toxic than CHOP. Clinical studies are evaluating the feasibility of combining the Treanda and Rituxan regimen with maintenance Rituxan.

Table 1. Types of Treatment

- R-CHOP [Rituxan, cyclophosphamide, hydroxydaunomycin (doxorubicin), Oncovin® (vincristine), and prednisone]
- VcR-CAP [bortezomib (Velcade), Rituxan, cyclophosphamide, doxorubicin (Adriamycin®) and prednisone]
- R-CHOP [Rituxan, cyclophosphamide, hydroxydaunomycin (doxorubicin), Oncovin (vincristine), and prednisone] with an autologous stem cell transplantation
- Maxi-R-CHOP, The Nordic Lymphoma Study Group Protocol [R-CHOP followed by higher doses of cytarabine, followed by an autologous stem cell transplant]
- R-hyperCVAD [Rituxan, cyclophosphamide, vincristine, doxorubicin (Adriamycin®), and dexamethasone alternating with high-dose cytarabine and methotrexate]
- R-hyperCVAD [Rituxan, cyclophosphamide, vincristine, doxorubicin (Adriamycin), and dexamethasone alternating with high-dose cytarabine and methotrexate] either with or without autologous stem cell transplantation
- B+R [bendamustine (Treanda®) and Rituxan]
- R-FCM [Rituxan, fludarabine (Fludara®), cyclophosphamide and mitoxantrone]
- R-DHAP [Rituxan, dexamethasone, cytarabine and cisplatin].
- R-CVP (Rituxan, cyclophosphamide, vincristine, and prednisone)
- R-CBP [Rituxan, cyclophosphamide, bortezomib (Velcade®) and prednisone]

Note: These are some of the combination chemotherapies. They may or may not be consolidated with an autologous stem cell transplant.

For older, less fit MCL patients (who often have coexisting disease), less intensive approaches are the best option. Single-agent oral Leukeran (chlorambucil) may be a good choice for frail elderly patients or for patients with serious comorbidities. Less aggressive treatment regimens such as low-dose Treanda in combination with Rituxan (B+R) may also be offered. The combination of oral chlorambucil with Rituxan may also be considered for these patients; the regimen is well tolerated in most patients. Some elderly frail patients may benefit from combination R-CVP (Rituxan, cyclophosphamide, vincristine, and prednisone), or even a newer regimen of R-CBP (Rituxan, cyclophosphamide, bortezomib (Velcade®) and prednisone).

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)."

Patients will be better prepared for their treatments if they know how a medication is administered. The drugs from combinations listed in Table 1 on page 4, are given in different ways including

- Intravenously (IV): Rituxan, doxorubicin, vincristine, methotrexate, cytarabine, fludarabine, mitoxantrone and cisplatin.
- IV or, less commonly, by mouth: cyclophosphamide
- By mouth: prednisone and dexamethasone.

The side effects of combination treatment 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, peripheral neuropathy (tingling, burning, numbness or pain in the hands or feet), changes in blood cell counts, infection, rash, diarrhea, shortness of breath, temporary loss of hair and other side effects. Patients may be less fertile after undergoing certain cancer treatments.

Talk to Your Doctor About Side Effects of Treatment. Side-effects management is important. If you are having any concerns about your side effects, talk to your doctor or nurses to get help. Most side effects can be managed with treatment that will not compromise treatment for your disease. In fact, aggressive management of side effects often leads to better treatment outcomes. Most side effects are temporary and resolve when treatment is completed.

For additional drug information, see the free LLS publication *Understanding Side Effects of Drug Therapy* and the Food and Drug Administration (FDA) drug information webpage at www.fda.gov/drugs/resourcesforyou/consumers/default.htm. Also, see *Treatments Under Investigation* on page 6.

Stem Cell Transplantation. Because outcomes with conventional chemotherapy have been disappointing, autologous stem cell transplantation has been combined with initial first-line treatment of MCL. 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 and stored (harvested). The harvested cells are frozen and then returned to the patient after he or she has received intensive high-dose chemotherapy either with or without radiation therapy. High-dose chemotherapy with autologous stem cell transplantation has resulted in high rates of clinical remission for MCL patients when used in first complete remission and may be an option for clinically symptomatic fit younger patients with few or no coexisting illnesses. Autologous transplantation combined with effective induction agents, including combinations of monoclonal antibodies and chemotherapy, may offer a longer remission in these patients. Recent research suggests that this procedure followed by maintenance Rituxan may improve progression-free survival. Some older fit patients may be candidates for autologous stem cell transplantation. High-dose chemotherapy and autologous stem cell transplantation is 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 medical indications and availability of a suitable donor. There is no specific age cutoff for stem cell transplantation. While allogeneic stem cell transplantation may not be used to routinely treat all forms of lymphoma, it has the potential to be curative for some patients with MCL. Reduced-intensity allogeneic transplantation may be an option for older patients. For more information, see the free LLS publication *Blood and Marrow Stem Cell Transplantation.*

Treatment for Patients with Relapsed or Refractory MCL

Some patients have a return of their disease after achieving remission. This is referred to as a "relapse." Some patients have disease that does not respond to initial treatment (called "refractory" MCL). There are a number of treatment options for relapsed or refractory MCL. Recent drug approvals for relapsed/refractory disease include: Velcade (bortezomib), which was first approved by the FDA for IV administration in MCL in 2006; it received additional approval for subcutaneous (injected under the skin) administration in

2012. More recently, the FDA granted approval for Revlimid® (lenalidomide) in June 2013 and the BTK inhibitor ibrutinib (Imbruvica®) in November 2013. Imbruvica is a very well-tolerated drug with minimal toxicity. Both drugs are given by mouth. The addition of Rituxan to Revlimid has achieved better results in patients with relapsed/refractory MCL than when Revlimid is given alone. This regimen is well tolerated. Velcade and/or Revlimid combinations may also be effective for patients with refractory MCL. However, depending on how sick the patient is, alternative chemotherapy regimens (e.g., Treanda based, gemcitabine based, fludarabine based) may be options. In select cases, an allogeneic stem cell transplant may be an alternative.

There are, additionally, several other new drugs are on the horizon. For a listing of investigational agents currently being studied for relapsed and refractory MCL patients, please see *Treatments Under Investigation*.

Treatments Under Investigation

Research for MCL over the past several years has resulted in better treatment options for patients; new therapies are constantly emerging. Patients may have the opportunity to take part in clinical trials. These trials, conducted under rigorous guidelines, help clinicians and researchers to determine the beneficial and adverse effects of potential new treatments. Studies are also conducted to evaluate new indications for therapies that are already approved for other cancers or types of diseases.

For more information about clinical trials, see the free LLS publication *Understanding Clinical Trials for Blood Cancers,* visit www.LLS.org/clinicaltrials or call our Information Specialists.

Some classes of novel therapies and drugs under investigation include

- Cell cycle inhibitors–Drugs of this type interfere with the cell division process that enables tumors to grow. One example of such a drug is PD-0332991 (palbociclib isethionate), an oral drug that decreases tumor cell proliferation. It is being studied as monotherapy and in combination with Velcade.

- Tyrosine kinase inhibitors–These drugs flip switches on the pathways of the B cells that are important to the cell staying alive. Tyrosine kinase inhibitors are a type of targeted therapy that blocks signals that tell a cell to grow and divide. This can slow or stop cancer cells from growing and, in some cases, may cause the cells to die. Oral drugs that are being studied include a phosphoinositide-3 (PI3) kinase inhibitor—idelalisb (Zydelig™), which may stop the growth of cancer cells and has shown clinical activity in relapsed MCL, is FDA approved for the treatment of chronic lymphocytic leukemia and for the treatment of refractory indolent NHL. The BTK inhibitor ibrutinib (Imbruvica®), which prevents the growth of malignant B cells, was approved for the treatment of MCL in 2013.

- Monoclonal antibodies–These agents provide a type of targeted therapy directed at specific proteins on the cell surface. Targeted therapies block the growth and spread of cancer by attacking specific cancer cells while minimizing harm to normal cells. Monoclonal antibodies can be used alone or to carry drugs, toxins, or radioactive substances directly to cancer cells. A number of new monoclonal antibodies are being investigated, including obinatuzumab (Gazyva™), which was recently approved for the treatment of previously untreated chronic lymphocytic leukemia (CLL), and ublituximab (TG-1101), which is being studied in all forms of CD20-positive lymphoma.

- Maintenance treatment (given to keep patients in remission and to prevent a relapse)–Patients who receive initial treatment with Rituxan plus chemotherapy and then receive maintenance Rituxan, may stay in remission longer than if they do not continue on Rituxan. One study of elderly patients who had responded to induction treatment but were not able to receive chemotherapy and an autologous stem cell transplant showed their duration of remission doubled after a period of maintenance Rituxan. Rituxan is also being studied as a maintenance therapy following combination chemotherapy to prolong response duration in patients with recurring or refractory MCL.

- Proteasome inhibitors–These drugs represent a targeted approach to therapy that minimizes toxicity. They affect cell pathways by blocking the activity of proteins that are needed for cell growth and survival. Velcade, which may also stop the growth of cancer cells by blocking blood flow to the tumor, is being studied together with Rituxan and combination chemotherapy (R-EPOCH [Rituxan plus etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin], R-CHOP or R-hyperCVAD) 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 with relapsed/refractory MCL. Kyprolis is designed to block cancer cells from repairing themselves, which may cause cell death.

- Stem cell transplantation–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. The results are being studied. Some patients showed prolonged disease-free survival.

- 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. They have demonstrated activity in MCL alone and in combination with other therapies. Examples of mTOR inhibitors currently 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 (e.g., Revlimid), monoclonal antibodies (e.g., Rituxan), alkylating agents (e.g., Treanda) and proteasome inhibitors (e.g., Velcade) for untreated and for relapsed/refractory MCL.
  - Everolimus (Afinitor®) is being studied in patients with advanced, refractory, or relapsed MCL. This drug is also being studied in combination with Revlimid and as single agent therapy in older patients. Afinitor exhibits antiangiogenic (cutting off the blood supply to cancer cells) activity, which may contribute to its anticancer activity.
- An alkylating agent–Bendamustine (Treanda) is FDA approved to treat chronic lymphocytic leukemia and indolent B-cell NHL that has progressed during or within 6 months of treatment with Rituxan or a Rituxan-containing regimen. The agent is being studied in combination with Rituxan and Torisel in patients who have relapsed or refractory MCL and in combination with Rituxan and Revlimid in older, previously untreated patients. Treanda is also being evaluated in a clinical study comparing the drug with R-CHOP or R-CVP for the treatment of MCL in elderly patients.
- Immunomodulators–These substances regulate the function of the immune system and have the capability of slowing the rate at which cancer cells grow and multiply. Thalidomide (Thalomid®) and Revlimid are both FDA approved to treat myeloma. Revlimid was also approved for the treatment of patients with relapsed or refractory MCL. These drugs act by modulating the immune system and by blocking the growth of blood vessels that allow cancer cells to grow (antiangiogenesis); they also have anti-inflammatory effects. These drugs are being studied in combination with Rituxan and/or other agents in patients who have relapsed or refractory MCL and in previously untreated patients.
- Radioimmunotherapy (RIT)–Radioimmunotherapy (RIT), a targeted therapy, combines the cancer killing ability of radiation therapy with the precise targeting capability of immunotherapy to deliver lethal doses of radiation directly to cancer cells. RIT directly targets and kills cancer cells and has fewer, less severe side effects than most high-dose conventional chemotherapies. In RIT, radioisotope (radioactive molecules) are attached to monoclonal antibodies, which bind to cancer cells, enabling a high dose of radiation to be delivered directly to cancer cells while decreasing the dose 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, given intravenously, is FDA approved for the treatment of two subtypes of NHL that are relapsed or refractory to conventional chemotherapy. Zevalin is in clinical investigations for the treatment of MCL. RIT is also being investigated as a component of high-dose therapy prior to autologous stem cell transplantation. RIT may prove to be feasible in post-induction therapy of elderly and unfit patients who have MCL.

A series of small molecules targeting cell death are being tested to treat MCL. These investigational agents include: Flavopiridol (alvocidib) (an inhibitor of cyclin-dependent kinases, specifically, of CDK1) and oral vorinostat (suberoylanilide hydroxamic acid/SAHA) an inhibitor of histone deactylases (a group of enzymes involved in the control of gene expression).

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 (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 progression-free period for patients with MCL is 20 months and the median overall survival is between 5 and 7 years. The prognosis for the blastoid variant of MCL is poor. This type of MCL typically progresses after chemotherapy; better treatments are needed. Improvements in therapy take several years of observation to determine the results of these new approaches. 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 country and in Canada. To find your chapter, visit our website at www.LLS.org or contact

The Leukemia & Lymphoma Society
1311 Mamaroneck Avenue
White Plains, NY 10605
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. Various resources are listed below. Use this information to learn more, to ask questions, and to make the most of your health care team's knowledge and skills.

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
- Visit: www.LLS.org/informationspecialists.

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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 education programs for patients, caregivers and healthcare professionals. For more information, please visit www.LLS.org/programs.

Co-Pay Assistance Program. LLS offers insurance premium and medication co-pay assistance for certain eligible patients. For more information, please

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

Online Blood Cancer Discussion Boards and Chats. Online discussion boards and moderated online chats can provide support and help cancer patients to reach out, and share information. For more information please visit www.LLS.org/getinfo.

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 with MCL are under way. 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 Specialists who can help conduct clinical-trial searches
- Visit: www.LLS.org/clinicaltrials.

Advocacy. LLS enlists volunteers to advocate for policies and laws to speed 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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