

Mantle Cell Lymphoma

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What is lymphoma?

Lymphoma is a cancer of the white blood cells, namely lymphocytes, that happen to constitute the lymphatic system. The two main types of lymphoma are Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). Lymphoma is the most common blood cancer and the third most common cancer of childhood. Lymphoma occurs when lymphocytes, a type of white blood cell, grow abnormally. The body has two types of lymphocytes: B lymphocytes, or B-cells, and T lymphocytes, or T-cells. Although both cell types can develop into lymphomas, B-cell lymphomas are more common. Like normal lymphocytes, those that turn malignant can grow in many parts of the body, including the lymph nodes, spleen, bone marrow, blood or other organs.

What is mantle cell lymphoma?

Mantle cell lymphoma (MCL) is a B-cell lymphoma that gets its name because mantle cell tumors are composed of cells that come from the “mantle” zone of the lymph node. Frequently, MCL is diagnosed as a stage 4 disease, often present in lymph nodes above and below the diaphragm and in most cases involves the gastrointestinal tract and bone marrow. MCL is a relatively rare disease, constituting only about 6 percent of all NHL cases in the United States (i.e., only about 3,000 cases per year in the U.S.). This lymphoma usually affects men over the age of 60.

How is mantle cell lymphoma diagnosed?

To confirm the diagnosis of MCL, doctors will first view a biopsy sample under the microscope, often complementing this step with sensitive molecular tests that detect alterations

in the genetic material of tumor cells in the biopsy tissue. Overproduction of a growth-promoting protein called Cyclin D1 (also called Bcl-1) is found in more than 90 percent of cases and is considered a very sensitive tool for diagnosing MCL. The overproduction of Cyclin D1 is caused by a molecular event called a genetic translocation, in which inappropriate shuffling of DNA directs cells to make large quantities of this growth-stimulating protein. Other molecular tests may also be used. One-quarter to one-half of MCL patients have higher than normal levels of certain proteins that circulate in blood, such as the enzyme lactate dehydrogenase (LDH) and the protein beta-2 microglobulin. Measuring levels of these proteins can often help gauge how aggressive a tumor is and may guide therapy decisions.

What treatments are available?

Mantle cell lymphoma is an aggressive form of NHL that requires combination chemotherapy. Like other forms of NHL, there is no consensus on the frontline or subsequent line treatments. Up-front treatments can range from simple R-CHOP to complex regimens like hyperCVAD, EPOCH and even stem cell transplant. MCL is considered a difficult cancer to treat. However, it is important to remember that survival times for individual patients can vary quite dramatically, since statistical figures can only describe the general features of a population. Recent research has unveiled novel combinations of chemotherapy, new biological therapies and combination regimens that show promise in treating MCL, and possibly, in improving survival from this lymphoma. In fact, in recent years, major advances are being made routinely to improve the treatment of mantle cell lymphoma.

Chemotherapy

Although there is no clear consensus about the best treatment for individual MCL patients, a common chemotherapeutic treatment approach that has been used is R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone). Recent studies suggest that combining chemotherapy regimens with the monoclonal antibody rituximab (Rituxan) improves patients' response rates and possibly overall survival. More intensive chemotherapy regimens are also being tried. One example is hyperCVAD-R (hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone, methotrexate, cytarabine and rituximab). Supplementing hyperCVAD with rituximab or stem cell transplantation has shown promising early results and although more intensive, may be better than R-CHOP for selected younger patients with the disease. HyperCVAD is usually administered as an inpatient in the hospital. Other combinations of drugs like a dose intense R-CHOP plus ICE chemotherapy (ifosfamide, carboplatin and etoposide) may be equally as active as hyperCVAD and don't require long hospitalizations.

Immunotherapy

Several clinical studies are investigating the effectiveness of immunotherapy, in which the power of the immune system is enlisted to fight cancer. Monoclonal antibodies, such as Rituxan, work by targeting and attaching to surface markers on lymphoma cells and gluing themselves on. This action triggers the patient's immune system to kill the cancer cells as it might attack any foreign invader, such as a bacterium or virus. Radioimmunotherapy is a modification of this approach, in which a monoclonal antibody is combined with a radioisotope particle, "arming" the antibody with a local source of radiation. After a monoclonal antibody hones in on its cancer cell target, radiation destroys it and nearby cancer cells in what is called a "crossfire effect." Two such antibody drugs, Iodine-131 tositumomab (Bexxar) and Yttrium-90 ibritumomab tiuxetan (Zevalin), have been approved to treat some types of NHL and are currently being tested against MCL. In one study, Bexxar is being tested in a sequential treatment with CHOP.

In addition to investigating various antibody-based treatments for use against MCL, researchers are also testing custom-made cancer vaccines, such as GTOP-99 (MyVax). This immunological treatment is a patient- and tumor-specific therapy that is based upon the genetic makeup of an individual

patient's tumor. Lymphoma vaccines are referred to as therapeutic vaccines because instead of preventing cancer, they treat lymphoma in minimal disease states in an effort to prevent recurrence. Such vaccines are usually given a few months after a patient completes a course of chemotherapy. Initial results using cancer vaccines to treat MCL appear promising, although researchers do not yet know whether they extend survival.

Hematopoietic Stem Cell (bone marrow) Transplantation

Bone marrow, the spongy material found inside bones, contains immature "stem" cells. These cells develop into three types of cells found in the blood: red blood cells that deliver oxygen to all parts of the body and take away the waste product carbon dioxide; white blood cells that protect the body from infection; and platelets that help blood clot. If very high doses of chemotherapy or radiation are used to destroy cancer cells, normal bone marrow is destroyed. A stem cell transplant can help restore healthy bone marrow. There are two sources of hematopoietic stem cells: allogeneic sources, in which patients receive bone marrow or stem cells donated by another person, and autologous sources, in which patients receive their own cells. Autologous stem cell transplantation (SCT) is far more commonly used than is allogeneic stem cell transplantation (SCT). High-dose chemotherapy coupled with SCT can be used for MCL patients who have failed their initial chemotherapy but are responsive to a second chemotherapy regimen, although some researchers feel that allogeneic SCT is better for patients who have had a relapse and that autologous SCT should only be used to treat patients as part of initial therapy. Mini-stem cell transplants are procedures in which hematopoietic stem cells are received from an allogeneic donor, but the chemotherapy administered is "minidose." These procedures are quite new and are therefore still considered investigational. Unlike a normal hematopoietic stem cell transplant in which high dose chemotherapy is administered, in these procedures the patient receives low or normal dose chemotherapy, just enough to allow the body to accept the donor cells. This approach is used to take advantage of the graft-versus lymphoma effect, in which the transplanted cells recognize the tumor as a foreign invader and activate immune cells to destroy it. Patients who experience a graft-versus lymphoma effect may remain in remission for a longer period. Also, because patients receive lower doses of chemotherapy, they may avoid some of the toxicities seen with higher dose chemotherapy.

Other treatments

Presently, there are many exciting new drugs that appear to have promising activity in MCL. Many of these therapies are based upon what scientists have learned about the biology of

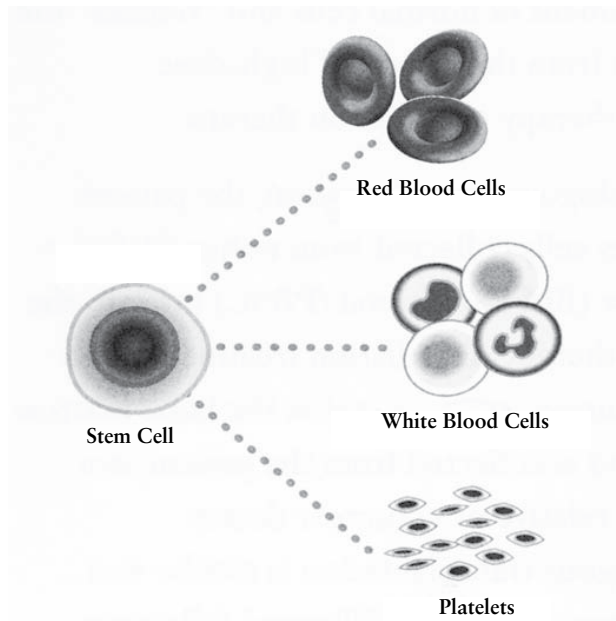


Diagram of stem cell maturation

human cells. For example, a new medication, called Velcade (bortezomib or PS-341), acts to disrupt a cellular process called the ubiquitin-**proteasome** pathway, which performs a critical role in eliminating proteins in normal and cancer cells. Velcade has been approved by the FDA for the treatment of patients with mantle cell lymphoma who have relapsed or refractory disease after at least one prior therapy. The approval is based on a clinical trial involving 155 patients with relapsed MCL. Velcade was also approved by the FDA in 2003 for the treatment of multiple myeloma, another blood cancer.

In addition, some physicians are exploring other ways to interfere with cancer cell growth. Originally used in the 1950's as a treatment for insomnia and morning sickness, a drug called thalidomide (Thalomid) is approved for use in treating complications of the chronic infectious disease leprosy. Thalidomide has become an important new drug for the treatment of myeloma, but also seems to demonstrate promising activity against MCL, especially in combination with Rituxan. Some researchers believe that thalidomide works, at least in part, by blocking the growth of blood vessels that nourish tumors, a process known as **angiogenesis**. Others believe it modulates the immune system.

Other drugs are also being investigated that show promise in treating this challenging disease. Scientists know that a protein called bcl-2 protects cancer cells from dying. They are testing new drugs that intentionally block bcl-2. One of these experimental drugs is called oblimersen (Genasense). This drug leads to the degradation of Bcl-2 messages in cancer cells, increasing their sensitivity to chemotherapy.

Another novel class of drugs that have recently emerged as having promising activity in MCL include the mTOR inhibitors. mTOR stands for the 'mammalian target of rapamycin'. Rapamycin is a naturally occurring compound that happens to inhibit mTOR quite effectively. mTOR plays an important role in turning on a host of proteins called transcription factors, which then can influence cell growth. Excessive activation of the mTOR pathway can lead to excessive cell growth, while inhibition of mTOR can lead to inhibition of cell growth and even cell death. Recently, Temsirolimus (previously known as CCI-779) has been demonstrated to induce responses in almost 40 percent of patients whose MCL had become resistant to other more traditional chemotherapies. These responses lasted about 6 months. Over the next several years, investigators will be combining this promising new drug with a host of other drugs like Rituxan and Velcade, to try and improve on the activity.

What about clinical trials?

Over 150 clinical studies are currently underway to test new treatments for MCL. The outcomes of these studies will point doctors to a broader array of effective therapies for this lymphoma. Doctors cannot know for sure whether a new treatment is safe, effective and better than standard therapy without testing new drugs in humans. Patient participation in clinical trials offers the quickest path to effective new treatments for cancer. If you choose to participate in a clinical trial, you may receive treatments unavailable to most patients. Moreover, trial patients are monitored very closely and as such, they benefit from a high standard of care. To find out more about participating in a clinical study, talk to your doctor, contact LRF's *Helpline and Clinical Trials Information Service* or search online for clinical trials at www.clinicaltrials.gov or www.cancer.gov/clinicaltrials.

How can I stay informed?

Attitude is a critical ingredient for coping with cancer. You are a partner in your treatment and many patients feel better and do better when they participate actively in their care. Ask questions, learn about your options and work closely with your doctor. If you are interested in talking to and learning from people who have had similar experiences, ask about any support groups in your area, consider joining the *Lymphoma Support Network* (LSN), a nationwide buddy program that matches patients or caregivers. For more information about this program, contact the LSN Coordinator at 800-500-9976 or support@lymphoma.org.

Together we can beat MCL

Once touched by cancer many patients devote themselves to helping others with cancer. Many people feel better when they know their actions are either directly helping others or are working to support research for lymphoma cures. LRF recently announced a record of nearly \$22 million to be spent on MCL research. Thanks to the generosity of several donors, 40 research projects specifically targeted to understanding MCL have been funded.

The LRF's Mantle Cell Lymphoma Initiative is going further with the establishment of the Mantle Cell Lymphoma Consortium, a group of physicians who are working on overcoming MCL. The Consortium is pursuing projects that will help to enhance the effectiveness of this research on MCL. The MCL Consortium developed a website www.mantlecelllymphoma.org which is a resource for MCL researchers and an information source for MCL patients.

The Consortium is also developing projects such as a Cell Bank, a repository for human mantle cells with specific characteristics. By creating a Cell Bank, the MCLC hopes to assist scientists who need these resources to carry out their research. MCL cells will be available from one easy to work-with source. The Consortium is also planning to fund cutting edge pilot clinical trials among other projects. This program has been supported by the Picower Foundation and by a second anonymous donor family. With the support of all these generous donors, the Lymphoma Research Foundation has become the leading supporter of MCL research in the U.S. With many people working to overcome MCL, having hope and staying optimistic can help you endure your cancer therapy and healing process.

Glossary of Terms

Allogeneic stem cell transplantation: A procedure in which patients receive bone marrow or stem cells donated by another person

Angiogenesis: The process of developing new blood vessels

Antisense therapy: An investigational genetic therapy that halts the production of specific proteins

Autologous stem cell transplantation: A type of bone marrow or stem cell transplantation in which a patient receives their own cells

Bcl-2: A protein that enhances tumor survival by stopping cancer cells from dying

Cancer vaccines: A type of immunotherapy that combines components of cancer cells with a patient's own natural defenses to fight the disease. These vaccines are custom-made, using a sample of the tumor that is obtained from each patient's lymph nodes

Cyclin D1: A growth promoting protein that is a sensitive molecular tool for diagnosing MCL

Hematopoietic stem cells: Immature cells found in bone marrow that can develop into different blood components: red blood cells; white blood cells; and platelets. These are one form of adult stem cells

Immunotherapy: A treatment that uses or stimulates the immune system to fight infection and disease, including cancer

Lymphatic system: The tissues and organs that store and carry lymphocytes that fight infection and other diseases

Monoclonal Antibody: A type of biologic therapy that acts specifically against a particular molecule on target cells. Monoclonal antibodies have been developed to help combat specific cancers, including some forms of non-Hodgkin and Hodgkin lymphoma

Proteasome: A normal cellular machine that breaks down old, wornout, and/or improperly folded proteins

Radioimmunotherapy: A type of immunotherapy that is prepared by attaching a radioactive isotope to a monoclonal antibody

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The Lymphoma Research Foundation (LRF) offers a comprehensive series of patient education and support programs including:

- *Lymphoma Helpline & Clinical Trials Information Service*
- *Lymphoma Support Network*
- Patient Aid Grant Program
- Publications and newsletters
- Informational teleconferences and webcasts
- In-person conferences
- National Chapter Network

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About LRF

The mission of the Lymphoma Research Foundation (LRF) is to eradicate lymphoma and serve those touched by this disease. The Foundation is the nation's largest lymphoma-focused voluntary health organization devoted exclusively to funding lymphoma research and providing patients and healthcare professionals with critical information on the disease. More than 85 cents of every dollar spent support research and programming. People affected by lymphoma can receive free personalized information tailored to their diagnosis, help with finding a clinical trial, and easy-to-understand information on lymphoma, current treatments, and promising research. Please call 800-500-9976, email helpline@lymphoma.org, or visit the website www.lymphoma.org