Mantle Cell Lymphoma

No. 4 in a series providing the latest information on blood cancers.

Highlights

- Mantle cell lymphoma (MCL) is one of several subtypes of B-cell lymphoma.
- MCL usually begins with lymph node enlargement; it can spread to other tissues such as the marrow, liver and gastrointestinal tract. Sometimes it can begin in a lymphocyte outside a lymph node, such as in 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 translocation between chromosomes 11 and 14.
- MCL is treated like other aggressive B-cell lymphomas with multidrug therapy, often five agents combined. Newer agents, such as bortezomib (Velcade®) can be used in patients who have progression in their disease. Clinical trials are expected to introduce improvements in current treatment approaches.
- Autologous stem cell transplant may be used to treat MCL. Myeloablative or nonmyeloablative allogeneic transplantation may be used if the patient is within the appropriate age range for an allogeneic stem cell transplant and has a matched related donor.

Introduction

Lymphoma is a type of cancer that begins in a lymphocyte, usually in a lymph node or occasionally in another organ. It is divided into two major categories: Hodgkin lymphoma and non-Hodgkin lymphoma (NHL). Mantle cell lymphoma, one of several subtypes of NHL, represents about six percent of all NHL cases in the United States. This fact sheet includes information about its diagnosis and management. Information about the lymphatic system is presented first to provide background for the reader.

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What are the roles of lymphocytes and the lymphatic system?
A lymphocyte is a type of white blood cell. Most lymphocytes are found in the lymph nodes (small bean-shaped structures located throughout the body) and other parts of the lymphatic system, such as the skin, marrow, spleen, thymus and areas of the gastrointestinal lining. The lymphatic system is part of the body's immune system.

The lymphatic system contains three main types of cells: T lymphocytes, B lymphocytes and natural killer (NK) cells. These cells move around the body in lymphatic vessels containing a milky white fluid that is rich in lymphocytes. This fluid is called "lymph" Lymphocytes continually circulate in the body through the lymphatic vessels, from which they can enter the blood or the tissues to respond to infections by bacteria, fungi or viruses. T and B cells work together to make antibodies to destroy infectious agents in the body. The antibodies coat the infectious agents, making them targets for destruction by other white cells called "neutrophils" or "monocytes," normally present in the blood and tissues. NK cells can recognize cells infected with certain microbes and can attack those cells and microbes directly.

Lymph nodes are considered to be one of the principal organs in the immune system. A lymph node has an outer region called the "cortex," which contains lymphoid follicles in which B cells are made. These follicles have an outer zone called the "mantle zone" in which recently made B lymphocytes are found. The spaces between follicles are rich in T lymphocytes The inner region of the lymph node is called "the medulla." It contains B and T cells that are on their way out of the node and into lymph vessels.

What is mantle cell lymphoma?
Mantle cell lymphoma (MCL) is the result of a malignant transformation of a B lymphocyte in the outer edge of a lymph node follicle, called the mantle zone. The transformed B lymphocyte (lymphoma cell) grows in an uncontrolled way and the accumulated lymphoma cells form tumors in lymph nodes leading to their enlargement. The lymphoma cells can enter the lymphatic channels and the blood and spread to other lymph nodes or tissues such as the marrow, liver and gastrointestinal tract.

There are nearly 59,000 new cases of NHL in the United States each year. MCL patients represent about six percent of all new cases of NHL per year or about 3,500 new cases. MCL occurs more frequently in older adults – the average age at diagnosis is the mid-60s.

What are the causes of mantle cell lymphoma?
About 85% of patients with mantle cell lymphoma (MCL) have a genetic change involving chromosome 11 and chromosome 14, called a "reciprocal translocation," and abbreviated as t(11;14). In a sense, this genetic alteration can be considered to be the cause of the disease, since it

may be a result of the constant mutations occurring in many cells, possibly independent of the effects of an outside (environmental) factor.

During the development of B lymphocytes, a break in chromosome 11 (at the site of the cyclin D1 gene) results in the transfer of a small segment of chromosome 11 to chromosome 14 (at the site of a gene that controls the formation of antibody molecules). Thus, a short segment of chromosomes 11 and 14 exchange places. This genetic change triggers the transformed B lymphocyte (lymphoma cell) to overproduce cyclin D1 – a protein that supports and directs cell division and growth. The resulting accumulation of mutant mantle zone B lymphocytes leads to the tumors of MCL. 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).

How is mantle cell lymphoma diagnosed?
All lymphomas are first diagnosed by the examination of the biopsy of affected tissue, usually a lymph node. In the case of mantle cell lymphoma: 1) Microscopic examination of tissue obtained by lymph node biopsy, for example, can discern that a lymphoma is present. Special studies can determine that the lymphoma cells: 2) Have surface markers of B cells. 3) Overexpress the cyclin D1 protein within the cells; or: 4) Contain the translocation 11;14.

These findings establish the diagnosis of MCL in almost all patients. The pathologist (a doctor who specializes in examining tissue and diagnosing disease) also grades the lymphoma cells seen in the biopsy to determine if the cells are likely to result in disease that progresses slowly (and may be more responsive to standard chemotherapy) or disease that is more aggressive (and can be less responsive to standard chemotherapy). In a minority of cases, the lymphoma is diagnosed principally by the appearance of the cells under the microscope and their B cell features – the t(11;14) is absent, but the cells have gene expression patterns that are very similar to those of classic MCL and overexpress cyclin D2 or D3 rather than D1. A special test called “gene expression analysis for lymphoma” is used to see the pattern of over- or underexpression of thousands of genes usually expressed in lymphocytes.

Signs and Symptoms
At the time of diagnosis most patients 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. In the gastrointestinal tract a condition known as “multiple small intestine polyps” may result from the lymphoma cell growth. MCL cells may invade the brain and spinal cord.

Patients with MCL may experience loss of appetite and weight loss, nausea and/or vomiting,

indigestion, abdominal pain or bloating, a feeling of "fullness" or discomfort due to an enlarged liver or spleen, pressure or pain in the lower back often extending down one or both legs, or fatigue due to anemia, which may develop.

Tests Useful in Staging

The extent of the disease or "staging" is determined to plan the best treatment. Tests used for staging MCL may include the following tests:

- *Complete blood counts* to assess the concentration of red and white cells and platelets
- *Bone marrow aspiration and biopsy* to identify if the disease has extended beyond the lymph nodes and into the marrow
- *Imaging studies*, including computed tomography (CT) scans of the chest, abdomen and pelvis, to see whether the disease is present in the deep lymph nodes, liver, spleen or in other parts of the body
- *Blood studies* to check levels of specific proteins in the blood, especially serum lactic dehyrogenase (LDH) and beta 2-microglobulin, which are indirect markers of disease extent and rate of progression.

What are some of the therapies used to manage mantle cell lymphoma?

A hematologist-oncologist who is experienced in treating mantle cell lymphoma in a cancer center is the best person to recommend specific treatment and manage the disease. Most MCL patients receive treatment following diagnosis and staging. For a small number of patients, who have slow-growing MCL and are otherwise well, clinicians may recommend a period of "watchful waiting" during which the patient is closely monitored, before treatment is started. In these cases, therapy begins when symptoms become troublesome or the disease shows signs of progression (for example, increasing lymph node size or new enlarged nodes).

There are a number of chemotherapy combinations used to treat MCL. Patients typically start with one of these combinations plus rituximab (Rituxan®). Rituximab is a monoclonal antibody, an agent that is made in the laboratory and works by recognizing and binding to antigens on the surface of MCL cells; rituximab specifically targets the CD20 antigen, present on B lymphocytes. Recent studies show that patients who are treated with chemotherapy plus rituximab have a higher initial response rate than with chemotherapy alone.

The most common approaches include:

- R-CHOP – rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone
- R-hyperCVAD – rituximab, cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose cytosine arabinoside and methotrexate

• R-FCM – rituximab, fludarabine, cyclophosphamide and mitoxantrone.

More aggressive chemotherapy treatments, such as hyperCVAD, may increase response rates, but these treatments can be very toxic and are typically reserved for healthier, often younger patients. If the disease has spread to the central nervous system, drugs may be administered directly into the fluid bathing the spinal canal. This is referred to as "intrathecal therapy."

Radioimmunotherapy (RIT)

Radioisotope particles can be combined with a monoclonal antibody to enhance its effectiveness. The radioactive compound attaches to the antibody and the radiation destroys neighboring cancer cells. Tositumomab/iodine I-131(Bexxar®) and yttrium 90 ibritumomab tiuxetan (Zevalin®) are being studied for the treatment of MCL.

Proteasome Inhibitors

Bortezomib (Velcade) is a proteasome inhibitor approved by the US Food and Drug Administration (FDA) for the treatment of patients with relapsed or refractory MCL. Proteasome inhibitors affect cell pathways by blocking the activity of proteins that are needed for cell growth and survival. Velcade® has important anticancer activity as a single agent and is being studied in clinical trials in combination with other agents.

Stem Cell Transplantation

An allogeneic transplant is the transfer of stem cells from one person to another following high-dose chemotherapy or radiation therapy. This type of transplant is generally available to patients less than age 60. The development of nonmyeloablative regimens may be an option for older patients (see the *Clinical Trials* section).

High-dose drug therapy and autologous stem cell transplantation (a procedure involving the harvesting of the patients' own stem cells, freezing the collection, then returning it to the patient after he or she has received intensive drug therapy) has resulted in high rates of clinical remission for MCL patients. Older patients who are in excellent physical condition are candidates for autologous stem cell transplantation.

Results of Therapy

There has been notable progress in the treatment of MCL over the last three 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 (relapse). Treatment resistance may develop, which means that patients become less responsive to chemotherapy.

The median progression-free period for patients with MCL is 20 months and the median overall survival is about four years. These figures do not reflect the effects of recent improvements in therapy because it takes several years of observation to determine the results of new approaches to treatment. Researchers continue to look for therapies that will prolong remissions and extend survival in patients with MCL.

Clinical Trials

Clinical trials explore new drugs, new treatment combinations or new uses for approved drugs for blood cancers and other diseases. New drugs and new combinations of therapies are needed to further improve outcomes and find cures for patients MCL. In addition, research to define predictive biomarkers to better identify MCL subtypes will help guide treatment decisions in the future, thereby improving patient outcomes.

Current information about specific clinical trials for mantle cell lymphoma can be obtained by calling the Information Resource Center of The Leukemia & Lymphoma Society at (800) 955-4572 or the National Cancer Institute at (800) 4-CANCER or (800) 422 6237.

Some therapies under study are mentioned earlier in this section on treatment. Others include:

Rituximab is active against residual MCL cells and is being studied as a maintenance therapy following combination chemotherapy to prolong response duration in patients with recurring or refractory MCL.

A number of new monoclonal antibodies, including bevacizumab (Avastin®) (in combination with R-CHOP for untreated MCL), alemtuzumab (Campath®), an anti-CD52 agent being used as part of a conditioning regimen in allotransplant, epratuzumab (anti-CD22) and anti-CTLA-4 (CD-152), are being investigated.

Bortezomib (Velcade®) is being studied together with rituximab and combination chemotherapy (R-EPOCH [Rituximab plus etoposide, doxorubicin, vincristine, cyclophosphamide, prednisolone], R-CHOP, R-hyperCVAD) in both untreated and refractory MCL.

Custom-made cancer vaccines, such as GTOP-99 (MyVax®), a patient-specific vaccine that does not prevent the disease, but may stimulate the immune system's attack on remaining MCL cells after initial therapy.

Nonmyeloablative allogeneic stem cell transplantation, which uses less intensive conditioning therapy prior to transplanting donor cells compared to a standard allogeneic transplant, are being studied. Study results vary; however, some patients showed prolonged disease-free survival.

Agents called "mTOR" inhibitors may work to slow or inhibit MCL by downregulating (reducing) cell expression of cyclin D1. They have demonstrated activity in MCL either alone or in combination with other therapies. Examples of mTOR inhibitors currently under investigation include:

- Temsirolimus for relapsed mantle cell lymphoma. This agent is also being studied in combination with rituximab.
- Everolimus (RAD001) is being studied in patients with advanced, refractory or relapsed MCL.

Thalidomide (Thalomid®) and lenalidomide (Revlimid®) act by modulating the immune system and by blocking the growth of blood vessels that allow cancer cells to grow (anti-angiogenesis). These drugs are being studied in combination with rituximab and/or other agents in patients with relapsed or refractory MCL

A series of small molecules targeting cell death have been developed and are appealing for the treatment of MCL. Some of these investigational agents include: flavopiridol, an inhibitor of cyclin D1 kinases, and oral suberoylanilide hydroxamic acid (SAHA), a new class of antitumor agents.

Is The Leukemia & Lymphoma Society funding research on mantle cell lymphoma?
The Society is funding a number of studies to help advance understanding of mantle cell lymphoma. Some of these studies are investigating:

- The role of cyclin D1 in lymphoma development and progression
- Ways to improve the diagnosis and treatment of MCL
- How cells maintain genetic stability by controlling the arrest and resumption of growth following chromosome breaks and genetic damage.

Resources

The Leukemia & Lymphoma Society

The Leukemia & Lymphoma Society is the world's largest voluntary health organization dedicated to funding blood cancer research, education, and patient services.

The Society has chapters throughout the country and in Canada. To find the Society chapter nearest you visit our Web site at www.LLS.org or contact:
The Leukemia & Lymphoma Society
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www.LLS.org

Through the Society's Information Resource Center, callers may speak directly with an Information Specialist, Monday-Friday, 9 AM-6 PM, ET at (800) 955-4572. To contact an Information Specialist, click on Live Help (10 AM-5 PM on the Society's Web site or email us at infocenter@LLS.org.

Information Specialists can answer general questions about diagnosis and treatment options, offer guidance and support, and assist with clinical trial searches for leukemia, lymphoma and myeloma.

The Society's Web site has information about how to find a clinical trial, including a link to the clinical trials search service of the National Cancer Institute.
The Society provides fact sheets and booklets that can be ordered via the 800 number or through the Free Materials section at www.LLS.org.

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