

Mantle Cell Lymphoma

Overview

Lymphoma is the most common blood cancer. The two main forms of lymphoma are Hodgkin lymphoma and non-Hodgkin lymphoma (NHL). Lymphoma occurs when lymphocytes, a type of white blood cell, grow abnormally. The body has two main types of lymphocytes that can develop into lymphomas: B-lymphocytes (B-cells) and T-lymphocytes (T-cells). These cancerous lymphocytes can travel to many parts of the body, including the lymph nodes, spleen, bone marrow, blood or other organs, and can accumulate to form tumors.

Mantle cell lymphoma (MCL) is a rare form of NHL, constituting only about 6 percent of all NHL cases in the United States (i.e., only about 3,000 cases per year). It is considered an aggressive B-cell lymphoma that usually affects men over the age of 60. Frequently, MCL is diagnosed at a later stage of disease and in most cases involves the gastrointestinal tract and bone marrow. The disease gets its name because mantle cell tumors are composed of cells that come from the “mantle zone” of the lymph node.

Overproduction of a growth-promoting protein called Cyclin D1 is found in more than 90 percent of MCL cases and is considered a very sensitive tool for diagnosing MCL. An inappropriate shuffling of DNA (called a translocation) causes the over-production of Cyclin D1, which contributes to the uncontrolled growth of these cancer cells. One-quarter to one-half of MCL patients also have higher than normal levels of certain proteins that circulate in the blood, such as the enzyme lactate dehydrogenase (LDH) and the protein beta-2 microglobulin. Measuring levels of these proteins, in addition to certain MCL tumor cell markers, can help gauge how aggressive an individual patient’s MCL is and may guide therapy decisions.

Treatment Options

The type of treatment selected for an MCL patient depends on the stage of disease, the age of the patient and the patient’s overall health. MCL is considered a difficult cancer to treat. However, a tremendous amount of progress has been made in the discovery of new treatments for the disease.

Watchful Waiting: Some patients present with asymptomatic,

slow-growing disease. Such patients can be initially managed with “watchful waiting” and deferred treatment until symptomatic progression.

Chemotherapy: Recent studies have shown that combining chemotherapy regimens with the monoclonal antibody rituximab (Rituxan) improves MCL patients’ response rates and possibly overall survival. For example, a common chemotherapeutic treatment approach used to treat MCL is R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone). Supplementing HyperCVAD-MTX/AraC (hyper-fractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone, methotrexate and cytarabine) with rituximab (Rituxan) or stem cell transplantation has also shown promising results. Although this treatment is very intensive, with considerable toxicities, it may provide longer response durations for selected younger patients with MCL compared to R-CHOP.

Proteasome Inhibitors: These drugs disrupt a molecular pathway that is critical for the elimination of proteins in both normal and cancer cells. Bortezomib (Velcade) is a proteasome inhibitor that has been approved by the United States Food and Drug Administration for the treatment of MCL patients who have received at least one prior therapy. Recent studies with bortezomib (Velcade) have demonstrated that the drug complements many conventional chemotherapy agents.

Transplantation: Bone marrow contains immature stem cells that develop into red blood cells, white blood cells and platelets. If very high doses of chemotherapy or radiation are used to destroy cancer cells, bone marrow is destroyed. A stem cell transplant (SCT) can help restore healthy bone marrow. There are two types of SCTs: allogeneic (patients receive stem cells from another person) and autologous (patients receive their own cells). SCT is being tested in clinical trials for younger MCL patients as consolidation therapy after initial induction treatment with chemotherapy plus rituximab. Reduced-intensity transplants (called non-myeloablative or mini-transplants) are procedures in which stem cells are received from an allogeneic donor, but the chemotherapy and/or radiation administered prior to the transplant is less intense (i.e., just enough to allow the body to accept the donor cells). The transplanted cells (the

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Last Updated June 2010

"graft") recognize the cancer as a foreign invader and activate immune cells to destroy it. Patients receiving reduced-intensity transplants may avoid some of the side effects seen with high-dose chemotherapy coupled with fully ablative allogeneic SCT.

Debate exists among researchers regarding which type of transplant (e.g., autologous versus allogeneic) is most efficacious and whether or when transplant should be used in the treatment of MCL. High-dose chemotherapy coupled with SCT can be used to treat MCL patients who have failed initial chemotherapy, but are responsive to a second chemotherapy regimen. 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.

Treatments Under Investigation

Alkylating Agents: Bendamustine (Treanda) is an alkylating agent that damages a cancer cell's DNA, ultimately resulting in cell death. Researchers are currently investigating the drug in combination with other drugs, such as rituximab (Rituxan), to treat MCL.

Antimetabolites: Gemcitabine (Gemzar) is an antimetabolite, a drug that interferes with cell growth, being tested in MCL patients. It is also being studied in combination with bortezomib (Velcade).

Bcl-2 Directed Therapies: Scientists know that a protein called bcl-2 protects cancer cells from dying. They are now testing new drugs that intentionally block bcl-2 either as single agents or in combination with existing chemotherapy regimens.

Immunotherapy: Monoclonal antibodies, such as rituximab (Rituxan), are a form of immunotherapy. They work by attaching themselves to specific protein targets on the surface of lymphoma cells, triggering the patient's immune system to locate and kill the cancer cells. Radioimmunotherapy (RIT) is a modification of this approach, in which a radioactive molecule is attached to the monoclonal antibody. After the monoclonal antibody attaches to the cancer cell, radiation from the radioactive molecule destroys it. Two RIT drugs, Iodine-131 tositumomab (Bexxar) and Yttrium-90 ibritumomab tiuxetan (Zevalin), have been approved for some types of NHL and are being tested in MCL.

Immunomodulatory Drugs: Immunomodulatory drugs (IMiDs) activate the patient's immune system to mount an immune response against the cancer cells inside the patient's body. Some IMiDs currently under investigation for MCL include lenalidomide (Revlimid) and thalidomide (Thalomid).

mTOR Inhibitors: Excessive activation of the mTOR (mammalian target of rapamycin) pathway can lead to excessive cell growth, while inhibition of mTOR can prevent cell growth and even cause cell death. An mTOR inhibitor currently under investigation for MCL is temsirolimus (Torisel). Researchers will soon be combining this promising new drug with a host of other drugs, like rituximab (Rituxan) and bortezomib (Velcade), to improve its activity.

Follow Up

MCL may return after treatment. Therefore, it is essential that patients work with their physician to create a follow-up care plan, which includes regularly scheduled tests to monitor the patient's health. For more information on relapsed/refractory MCL, view the *Mantle Cell Lymphoma: Relapsed/Refractory* fact sheet on LRF's website (lymphoma.org).

Participating in Clinical Trials

Clinical trials are crucial for identifying effective drugs for lymphoma patients. Patients interested in participating in a clinical trial should talk to their physician. Contact the Lymphoma Research Foundation's *Helpline* for an individualized clinical trial search by calling (800) 500-9976 or emailing helpline@lymphoma.org.