UNDERSTANDING
Mantle Cell Lymphoma (MCL)

LYMPHOMA CANADA

Overview

Lymphoma is the most common form of blood cancer. Lymphoma occurs when cells of the immune system called lymphocytes, a type of white blood cell, grow and multiply uncontrollably.

WHAT ARE LYMPHOCYTES?

Lymphocytes are a type of white blood cell and are a major part of the lymphatic system. Together with other cells of the immune system, they work to fight infection and prevent disease. Lymphocytes can be found in the blood and bone marrow; however, most of them are normally circulating in the lymphatic system.

There are two main types of lymphocytes that can develop into lymphomas: B lymphocytes and T lymphocytes. The types of cells that become cancerous in mantle cell lymphoma (MCL) are B lymphocytes (B cells). B lymphocytes make antibodies to fight infections. They are called B cells because they mature in the bone marrow.

There are over 80 different subtypes of lymphoma. They fall into two main categories:

- Hodgkin lymphoma (HL)
- Non-Hodgkin lymphoma (NHL)

MCL is a type of NHL. NHLs are approximately eight times more common than HL – 85% of all lymphomas are NHLs. One of the main differences between HL and NHL is the presence of Reed-Sternberg cells which are large abnormal lymphocytes that can be detected under a microscope. Reed-Sternberg cells are typically present in Hodgkin lymphoma and are absent in Non-Hodgkin lymphoma.

NHL is further sub-categorized by 'grade':

- Low-grade: indolent (or slow-growing) NHLs
- Intermediate or high-grade: aggressive (or fast-growing) NHLs

Indolent lymphomas develop more slowly than aggressive lymphomas. Patients usually do not show symptoms until later, often as the disease progresses, and may therefore not require immediate treatment. Aggressive lymphomas on the other hand develop much more rapidly. Patients will usually experience symptoms from the onset of the disease and may require immediate and more intensive treatment.

Mantle cell lymphoma can be slow-growing (indolent) or fast-growing (aggressive). MCL can be classified into four types which differ in genetic changes (abnormal changes to genes, a unit of heredity) and clinical behaviour: leukemic non-nodal, classic, blastoid, and pleomorphic. The blastoid and pleomorphic types are considered to be the more aggressive types of MCL.

Mantle cell lymphoma gets its name because it develops in the outer region of a lymph node called the mantle zone. MCL can also affect organs or tissues other than the lymph nodes (called extranodal sites) including the spleen, bone marrow, kidneys, liver and gastrointestinal tract. Only rarely does MCL spread to the brain and spinal cord; this is called secondary central nervous system (CNS) lymphoma and is more likely to occur during a relapse than at initial diagnosis.

In more than 90% of MCL patients, there is an overproduction of a protein called Cyclin D1. When functioning normally, Cyclin D1 keeps a healthy balance of cells in the body. When genetic changes happen, this can result in an overproduction of Cyclin D1 leading to the division and growth of cancer cells.

Who gets MCL?

MCL is relatively uncommon and accounts for approximately 5% to 10% of all NHL cases. It most commonly affects men in their early to mid-sixties, although women may also be affected. MCL incidence is highest amongst Caucasians. Although the reasons for getting MCL are still unknown, there are risk factors that can predispose people to developing lymphoma including lifestyle and occupational risk factors, family history, viruses and molecular risk factors.

Symptoms

The most common symptom of mantle cell lymphoma is a painless swelling in the neck, armpit, and groin region(s), caused by enlarged lymph nodes. Often, lymph nodes in more than one area of the body are affected.

Enlargement of the spleen (splenomegaly) or liver (hepatomegaly) is relatively common for MCL patients. This may cause the patient to experience bloating or fullness after eating only small amounts of food. It can also cause abdominal pain, diarrhea, and vomiting.

Some patients may also experience symptoms due to reduced blood cell levels. MCL cells that grow in the bone marrow can crowd out and disrupt the production of normal, healthy blood cells. Many of the symptoms that can occur due to your MCL are a result of altered blood cell levels. Low levels of healthy red blood cells can lead to a condition called anemia, causing weakness and fatigue. Low levels of white blood cells (neutropenia) can make it difficult for the body to fight infection and can lead to a higher infection rate. A low platelet count, called thrombocytopenia, can cause increased bleeding and bruising.

Patients may also experience a group of symptoms called **B symptom**s. In the case of lymphoma, B symptoms refer to a specific set of symptoms that may help to predict how your lymphoma will progress.

B SYMPTOMS ARE:

- Fever with temperatures above 38˚C (100.4˚F), without any sign of an infection;
- Night sweats, enough to drench your pajamas or bedding;
- Weight loss without trying (at least 10% of your body weight over 6 months).

If your MCL has spread to the brain and spinal cord (known as the central nervous system), symptoms could include headaches, dizziness and confusion.

Diagnosis

MCL is usually widespread at the time of diagnosis. Doctors will need the results of different tests to confirm if you have MCL. The diagnosis of MCL is typically confirmed by a lymph node biopsy. This type of biopsy involves removing a sample of tissue (cells) from the lymph node. The removed tissue is then sent to a lab where it is examined under a microscope by a hematopathologist (a doctor who specializes in diagnosing diseases of the blood and bone marrow). A Cyclin D1 test will likely be performed on your lymph node tissue. This type of biopsy procedure can usually be performed under local anesthetic.

Other tests may also be performed to confirm your diagnosis. Because MCL is a blood cancer, it is important to look at the entire body to find all of the lymphoma. This is usually done with blood tests and imaging scans which can include a whole-body computed tomography (CT) scan, positron emission tomography (PET) scan, and/or magnetic resonance imaging (MRI) scan. A bone marrow biopsy may also be performed to look for the presence of lymphoma cells in the bone, and sometimes a spinal tap (lumbar puncture) may be performed to determine if there are lymphoma cells in the brain and spinal cord.

Staging

Staging describes a cancer based on how much cancer is in the body and where it is located when first diagnosed. MCL is staged based on the findings from your clinical examinations. Knowing the stage of your lymphoma helps your doctor determine the extent of your disease and monitor its progression over time.

Your MCL may be staged using the Ann Arbor Staging System. The stage is determined by the number and location of lymph nodes affected, whether the affected lymph nodes are above, below or on both sides of the diaphragm (the large, dome-shaped muscle under the ribcage that separates the chest from the abdomen) and whether the disease has spread to the bone marrow or to other organs such as the liver.

THERE ARE FOUR MAIN STAGES:

- **Stage I** The lymphoma is in one group of lymph nodes or one extranodal site
- **Stage II** The lymphoma is in two or more groups of lymph nodes on the same side of the diaphragm
- **Stage III** The lymphoma is in nodes both above and below the diaphragm
- **Stage IV** The lymphoma is widespread and found in multiple areas throughout the body including nodal and extranodal sites

Stages I and II are considered early stages. Stages III and IV are considered advanced stages.

YOUR DOCTOR MAY ALSO ADD A SINGLE LETTER TO THE STAGE:

- **A** generally means the patient has not experienced any troublesome symptoms
- **B** means the patient has experienced B symptoms (fever, night sweats, weight loss)
- **X** means the patient has bulky disease (large tumours)
- **E** means the patient has extranodal disease (disease outside of the lymph nodes)

Prognosis

WHAT IS PROGNOSIS?

Prognosis is the medical term used to describe how the disease will progress, how well the patient will respond to treatment, and the likelihood of recovery. It is usually based on information gathered from thousands of other patients who have had the same disease which provides a general idea of what to expect when a patient is diagnosed with MCL. However, it is important to remember that no two patients are alike and that it is not possible to accurately predict what will happen to a specific patient.

MANTLE CELL INTERNATIONAL PROGNOSTIC INDEX (MIPI)

Your doctor may also give you a prognostic score using the Mantle Cell International Prognostic Index (MIPI). The MIPI is a clinical tool developed by oncologists to aid in predicting the prognosis (outcome and survival) of patients with MCL.

The MIPI was developed based on individual risk factors including age, lactate dehydrogenase (LDH) levels, leukocyte (white blood cell) count, and the Eastern Cooperative Oncology Group (ECOG) performance status which provides a score based on a patient's ability to care for themselves and continue with daily activities.

Some risk factors of MIPI include:

- Age 50 years and older;
- Serum lactate dehydrogenase (LDH) level above normal;
- White blood cell count ≥ 6.7 x 10^9/L;
- ECOG performance status ≥ 2.

Using a specific formula, MIPI generates a prognostic score. This score helps identify whether a patient is low-risk (score < 5.7), intermediate-risk (score 5.7 to < 6.1) or high-risk (score ≥ 6.2). There may be additional prognostic factors that are important in determining the outcome and survival of a patient. These include gene expression levels, as well as a marker of abnormal cell growth called the Ki-67 index.

Treatment Options

Some patients diagnosed with mantle cell lymphoma have a type that grows quite slowly (this is known as the 'indolent form'). In this form, the lymphoma cells are often found in the bloodstream, where the lymph nodes are small or do not grow rapidly. If you have this type of MCL, your doctors may suggest the 'watch and wait' approach.

WHAT IS 'WATCH & WAIT'?

Many people newly diagnosed with indolent MCL may not need immediate anti-cancer treatment. Indolent MCL often progresses slowly and may not cause any problems for a period of time. Instead of immediate treatment, patients will be regularly monitored by their oncologist for months or years until the cancer changes and treatment is considered necessary. This approach is called 'watch and wait' , 'watchful waiting' or 'active surveillance'. Watch and wait is a standard treatment approach for those who have no symptoms, and additionally lets you avoid harmful treatment related side effects when treatment may not be necessary.

Once a patient has been treated, the watch and wait phase starts again, as their oncologist will begin to monitor them for a potential return of their cancer. Throughout the watch and wait period, you doctor will ask you whether you notice any changes in your current symptoms or if you are experiencing any new symptoms. They may also perform a physical examination, blood tests, and imaging scans to assess your response to treatment.

Some patients are concerned about the watch and wait approach and would rather receive immediate treatment following their diagnosis. Clinical trials for early-stage or slow-growing stable cancers have compared the watch and wait approach with immediate treatment. These trials have shown that patients that are monitored through watch and wait do as well or better than those given treatment immediately when treatment is likely to not improve outcomes or survival, and instead cause harmful or toxic side effects.

More often, mantle cell lymphoma is diagnosed as an aggressive type that grows rapidly, and so it is treated like a high-grade lymphoma and will require treatment following diagnosis. The first-line treatment for MCL is usually a combination of chemotherapy drugs, typically chemotherapy in combination with the antibody therapy, **rituximab (Rituxan)**. The treatment option selected will depend on the patients' age and level of fitness which measures their health and level of activity..

For younger, more fit patients, the standard treatment approach includes Rituximab + Chemotherapy, followed by an autologous stem-cell transplant (infusion with your own stem-cells). Options for chemotherapy regimens can include:

- **R-CHOP** (rituximab [Rituxan], cyclophosphamide, doxorubicin [Hydroxydaunorubicin], vincristine [Oncovin], prednisone)
- **R-DHAP** (rituximab [Rituxan], dexamethasone, cytarabine [Ara C], cisplatin)
- **B-R** (Bendamustine, rituximab [Rituxan])
- **HyperCVAD** (cyclophosphamide, vincristine [Oncovin], doxorubicin [Adriamycin], dexamethasone, methotrexate, cytarabine)
- **EPOCH** (etoposide [Vepesid], vincristine, doxorubicin, cyclophosphamide and prednisone)

For older, less fit patients, chemotherapy regimens can include:

- **B-R**
- **R-CHOP**
- **CVP** (cyclophosphamide, vincristine and prednisone) or **R-CVP** (CVP + Rituximab)

These drugs are typically administered intravenously (into a vein) which is performed in the hospital. A central-line, which is a catheter placed in a large vein, may be used to administer chemotherapy drugs and draw blood for testing. The chemotherapy is usually given in cycles of 2 to 4 weeks. A cycle includes treatment days followed by a period of rest and healing. The number of cycles you receive (called the 'course' or 'regimen') depends on the recommendation of your medical team based on your test results. Many patients will be able to receive their treatment as an out-patient, which means you will not have to stay in the hospital overnight.

Patients that have responded to their initial treatment may receive prolonged treatment with rituximab, called rituximab **maintenance therapy**. This means that patients who have received treatment for MCL and have achieved remission (complete or partial remission) may benefit from prolonged administration with rituximab (generally administered every three months for a period of two years). Rituximab maintenance therapy has been shown to maintain the response from the initial therapy and may improve the survival of patients with MCL.

Mantle cell lymphoma patients can also receive treatment with radiation therapy, small molecule targeted therapies, and other newer treatments either as stand-alone treatments or in combination with a chemotherapy regimen.

For some patients, the initial treatment is effective and the MCL does not return after treatment. However, for patients in whom the disease becomes refractory (does not respond to treatment) or relapses (returns after treatment), further therapies may be required. These therapies can range depending on your age and other health factors. Some patients may be treated with another chemotherapy combination with rituximab. Other patients may receive treatment with BTK inhibitors such as Ibrutinib or Zanubrutinib or Acalabrutinib. Additional chemotherapies or other drug treatments, stem-cell transplantation, radiation therapy, or newer drugs available through a clinical trial, may be used as a second-line or later treatment. **Chimeric Antigen T-Cell Therapy (CAR-T)** is a type of immunotherapy that is being tested in the relapsed/refractory setting. This treatment involves the extraction of a patient's immune cells (in particular the T Cells) that are then changed in a laboratory so that they will specifically attack the patient's lymphoma cells when re-infused. A patient may require multiple lines of therapy if their lymphoma relapses or is refractory to their previous treatment(s).

Patients with relapsed or refractory MCL are often encouraged to participate in clinical trials so that they can receive newer treatments that are not yet on the market. Clinical trials are crucial for establishing more effective, less toxic treatments for patients. You should consult your medical team for more information on whether a clinical trial is an appropriate treatment option for you.

Treatment Side Effects

Many people may be frightened to learn that there can be side effects associated with the therapies they may take to treat their lymphoma. However, it is important to understand that:

- Not all patients who receive therapy experience side effects;
- Side effects are not always severe, they can be mild;
- Different therapies have different side effects;
- There are many effective treatments that can reduce side effects or prevent them from happening altogether.

Some of the most common side effects of chemotherapy include decreased blood cell production (myelosuppression), fatigue, vomiting, diarrhea, loss of appetite, change in taste, hair loss, "chemo-brain" (cognitive impairment(s) that cause difficulties with concentrating and remembering) and peripheral neuropathy (affects nerve endings causing tingling and numbness).

Most side effects are short-lived, but some can last for a few weeks or months after treatment has finished. Occasionally, side effects can be permanent. Some side effects can start long after treatment has finished. These are called late side effects. Your doctor will talk to you about any potential side effects before you start treatment.

Depending on the side effects you experience and how strongly you feel them, you might not be able to maintain your usual level of activity during and following treatment. You may need to set aside more time for rest and healing. Additionally, depending on the severity of your side effects related to a therapy, your doctor may suggest to stop your treatment and can change your treatment to one that may not cause as many, or any, side effects.

Follow-Up Care

Use the time during your follow-up appointments to talk to your medical team about any changes or problems you notice and any questions or concerns you may have about your health after treatment. If you notice any change in your signs and symptoms between follow-up appointments, be sure to contact your medical team right away. Once you have completed active treatment, you will likely be given a follow-up care plan to monitor your response to treatment and recovery, as well as to watch for late effects (side effects that develop months or years after treatment) or a potential recurrence. Follow-up care for your MCL lymphoma is often shared between your cancer specialists and your family doctor. Your medical team will work with you to decide on the correct follow-up care plan to meet your needs.

Follow-up care after treatment is an important part of your cancer care. It is very important to go to all of your follow-up appointments. Your schedule of visits and the tests and procedures that you will undergo during your follow-up are tailored to your individual lymphoma.

Your doctor will also tell you to watch for specific signs or symptoms of relapse or transformation. These signs and symptoms may include symptoms associated with altered blood cell levels and counts, swelling of the lymph nodes, and problems with circulation. If you begin experiencing B symptoms (fever, unexplained weight loss, and drenching night sweats), that may be a sign that your lymphoma has transformed. Doctors may perform additional testing including blood tests and imaging scans to confirm if your lymphoma has relapsed.

YOU DON'T HAVE TO FACE LYMPHOMA ALONE.

Lymphoma Canada connects patients, their family and friends, medical professionals, researchers, volunteers and donors, to build a strong lymphoma community.

For more information please visit lymphoma.ca or call 1-866-659-5556, or email us at info@lymphoma.ca.

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