UNDERSTANDING
Splenic Marginal Zone Lymphoma (SMZL)

LYMPHOMA CANADA

Overview

Lymphoma is the most common form of blood cancer. Lymphoma occurs when cells of the immune system called lymphoctes, 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 splenic marginal zone lymphoma (SMZL) 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)

SMZL is a type of NHL. NHLs are approximately eight times more common than HL – 85% of all lymphomas are NHL. 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

SMZL is an indolent lymphoma. Indolent lymphomas develop more slowly than aggressive lymphomas. Patients with indolent lymphoma 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.

SMZL lymphoma is one of three subtypes of marginal zone lymphoma (MZL); the other two types are nodal marginal zone lymphoma (NMZL) and extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT) lymphoma. SMZL develops in the spleen (an organ that filters your blood and destroys old blood cells), whereas NMZL and MALT lymphomas originate in the lymph nodes and in lymphoid tissues in the mucosa (a protective layer of tissue that surrounds organs and cavities), respectively.

They are called "marginal zone lymphomas" as they develop at the edge of normal lymphoid tissues called the marginal zone. The marginal zone of certain tissues including the mesenteric lymph nodes (located along the inside of your abdomen) and the spleen, are more commonly affected because they are frequently exposed to external antigens (substances that trigger an immune response), which over time can harm the tissue causing lymphoma to develop in this region.

Who gets SMZL?

SMZL is a rare lymphoma that accounts for less than 2% of all NHL cases and approximately 8% of all MZL cases. It most commonly affects older adults aged 60 years and older. SMZL rarely occurs in those under the age of 50 years. It occurs more frequently in men than women. It also is more common in those who have been infected by the Hepatitis C virus or Kaposi sarcoma-associated herpesvirus (KSHV).

Symptoms

A quarter of patients diagnosed with SMZL are asymptomatic (do not have any symptoms) at the time of diagnosis. For the remainder of patients that do show symptoms at diagnosis, the most common symptom of SMZL is an enlarged spleen, referred to as splenomegaly. This may cause patients to experience bloating or fullness after eating only small amounts of food. It can also cause abdominal pain, diarrhea, and vomiting. Sometimes, SMZL can also cause enlargement of the liver (hepatomegaly). Unlike most lymphomas, SMZL rarely causes enlarged lymph nodes.

In SMZL, the bone marrow is often involved, which can lead to symptoms associated with neutropenia (low white blood cell count), anemia (low red blood cell levels), and/or thrombocytopenia (low platelet levels).

Patients may also experience a group of symtoms called **B symptoms**, however this is uncommon for this type of lymphoma. In the case of lymphoma, B symptoms usually 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).

Diagnosis

SMZL is often difficult to diagnose as it closely resembles other types of lymphoma. Therefore, doctors usually need the results of various tests to determine if you have SMZL. Sometimes, the same test may be performed more than once to confirm your diagnosis.

SMZL is usually diagnosed using a combination of blood tests and a bone marrow biopsy. Blood tests are used to look for abnormal lymphocytes or antibodies in the blood. A bone marrow biopsy involves removing a sample of bone marrow. 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). This type of biopsy procedure can usually be performed under local anesthetic.

Sometimes, patients with an enlarged spleen (splenomegaly) will require their spleen to be removed for testing. This procedure is called a splenectomy. You can live without a spleen, but you will have a reduced ability to fight infection.

Other tests may also be performed to confirm your diagnosis. Because SMZL lymphoma 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.

Staging

Staging describes a cancer based on how much cancer is in the body and where it is located when first diagnosed. SMZL is staged based on the findings from your clinical examinations including your blood work, bone marrow test, and imaging scans. Knowing the stage of your lymphoma helps your doctor determine the extent of your disease and monitor its progression over time.

Your SMZL 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 extra nodal sites

Stages I and II are considered early stages. Stages III and IV are considered advanced stages. SMZL is usually diagnosed at an advanced stage due to the nature of this lymphoma and its involvement of the bone marrow and the spleen.

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 SMZL. 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.

Unlike other types of lymphoma, there is no official scoring system developed by oncologists for SMZL to aid in predicting a patient's prognosis (outcome and survival). Generally, patients have a favorable outcome if diagnosed with SMZL. However, there are some clinical features that may predict a worse outcome.

These include:

- Anemia (low red blood cell count)
- Elevated lactate dehydrogenase (LDH)
- Low albumin levels

A poor response to treatment, with a short amount of time between treatment completion and lymphoma progression, is also concerning feature that may predict a poor prognosis.

Treatment Options

Treatment for SMZL depends on whether you experience any symptoms. Asymptomatic patients (patients that do not experience any symptoms) and patients with blood counts within normal range, may undergo a 'watch & wait' approach where they are closely monitored for symptoms that may indicate disease progression, rather than receive immediate treatment which may not improve outcome and survival.

WHAT IS 'WATCH & WAIT'?

Many people newly diagnosed with SMZL may not require immediate anti-cancer treatment. SMZL often progresses slowly and may not cause any problems for a period of time. Therefore, instead of receiving 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 will start again, and their oncologist will begin to monitor them for a potential return of their cancer. Throughout the watch and wait period, your 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.

The development of certain symptoms will suggest moving from a watch and wait approach to treatment. These symptoms can include symptomatic or progressive splenomegaly, low blood cell counts or symptomatic lymph node enlargement.

If you do require treatment, you will likely be treated with antibody therapy, specifically with the monoclonal antibody, **rituximab**. Rituximab may be used alone or in combination with the following chemotherapy options. Treatments options can include:

Single-agent chemotherapy:

- **Chlorambucil** (Leukeran)
- **Bendamustine** (Treanda)
- **Fludarabine** (Fludara)

Combination chemotherapy:

- **CVP** (cyclophosphamide, vincristine [Oncovin], prednisone)
- **CHOP** (cyclophosphamide, doxorubicin [Hydroxydaunorubicin], vincristine [Oncovin], prednisone)
- **FC** (fludarabine and cyclophosphamide)

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.

If you have an enlarged spleen, you may require your spleen to be removed if it has not been already. This procedure is called a **splenectomy**. After a splenectomy, symptoms of SMZL usually decrease significantly. You can live without a spleen, but you will have a reduced ability to fight infections. Therefore, you will need to take increased precautions to reduce your risk of future infections.

Patients who have the Hepatitis C virus or another virus linked with SMZL will likely receive treatment with anti-viral drugs. Treating the virus can reduce the symptoms associated with SMZL, and patients may not require further treatment.

For some patients with SMZL, the initial treatment may be effective at controlling the lymphoma. 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 include other chemotherapies or drug treatments, stem-cell transplantation, radiation therapy, or newer drugs available through a clinical trial. 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 SZML 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 drug, 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.

Transformation

Approximately 10-20% of patients with SMZL will have their lymphoma change into a more aggressive lymphoma, often referred to as histologic transformation. A transformed lymphoma is one that was initially diagnosed as indolent (slow-growing), such as SMZL, but then later develops into an aggressive (fast-growing) disease. Transformation typically occurs within 2-6 years after the lymphoma was initially diagnosed, however it can occur at any time. As transformed lymphomas are more aggressive in their behavior, they can require different treatments than what you may have received previously for your SMZL.

Follow-Up Care

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 SMZL 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.

SMZL will likely relapse (come back) after treatment in many people. Your doctor will tell you to watch for specific signs or symptoms of relapse or recurrence. Doctors may perform additional testing including blood tests and imaging scans to confirm if your lymphoma has relapsed or transformed.

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.