Understanding Lymphoma and Chronic Lymphocytic Leukemia (CLL)

Marginal Zone Lymphoma

Lymphoma Research Foundation

Marginal zone lymphomas (MZLs) are a group of indolent (slow-growing) B-cell non-Hodgkin lymphomas (NHLs), that develop in a part of the lymph node (small bean-shaped structures that help the body fight disease, Figure 1) tissue called the marginal zone.

MZL is the third most common indolent lymphoma and accounts for approximately 5 to 10% of all NHLs. The number of new cases of MZL increases with age, but the average age at diagnosis depends on the type of MZL (see below).

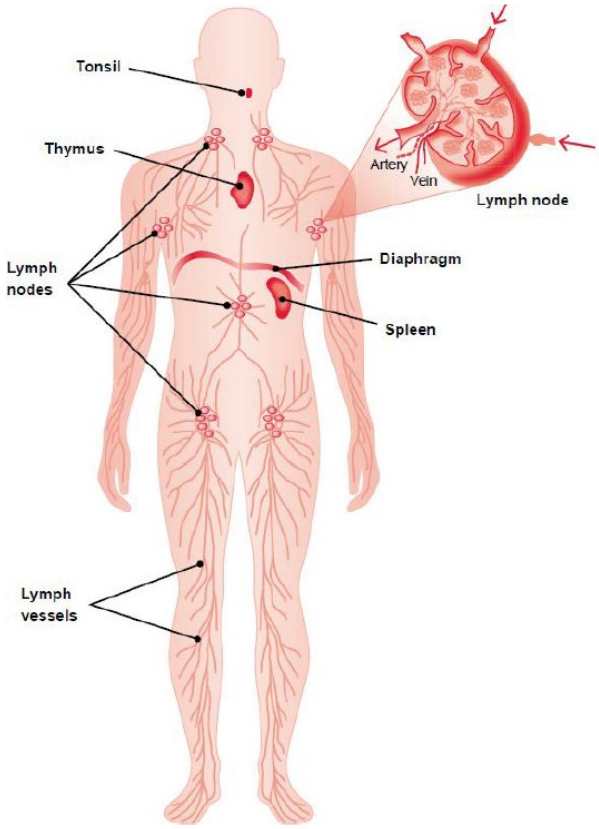

Figure 1: The *lymphatic system* (tissues and organs that produce, store, and carry white blood cells) and lymph nodes.

Symptoms depend on the tumor location (where the tumor is located in the body) and the extent (cancer stage and how far it has spread) of the disease. The most common symptoms associated with all forms of the disease include:

- Swollen lymph nodes – a lump that you can see or feel.
- Tiredness.
- Skin rash.
- Chest or abdominal pain.
- Night sweats.
- Weight loss.
- Fever.

Subtypes of MZL

Mucosa-associated lymphoid tissue (MALT) lymphoma or extranodal MZL is the most common form of MZL (61% of all MZL cases). This type of MZL affects tissues outside the lymph nodes (extranodal tissues) like the mucosa (inner lining) of some internal organs and body cavities. Listed below are the organs where MALT lymphomas are found:

- Stomach (called *gastric* MALT).
- Small intestine, salivary glands, thyroid, breast, around the eye (ocular adnexa lymphoma [OAL]), lung and skin (called *non-gastric* MALT).

MALT lymphomas often appear as a result of chronic inflammation (slow, long-term body response to infection lasting for prolonged periods of several months to years) caused by infection (with bacteria) or autoimmune conditions (the body's immune system starts attacking its own healthy cells) such as Hashimoto's thyroiditis or Sjogren's syndrome. In some patients, this might increase the risk of them developing into lymphoma cells. However, most patients with these autoimmune diseases will not develop MALT.

The bacteria that are known to cause MALT lymphoma include:

- *Helicobacter pylori*, which causes chronic inflammation of the stomach and gastritis.
- *Chlamydia psittaci*, which can cause orbital MALT lymphoma.
- *Campylobacter jejuni*, which causes Mediterranean abdominal lymphoma (or immunoproliferative small intestinal disease), often originated in the abdomen. It is a type of MALT lymphoma that affects young adults in eastern Mediterranean countries.

Nodal MZL is a rare type of MZL (30% of all MZL cases) that occurs within the lymph nodes.

Splenic MZL is the rarest form of MZL (9% of all cases) and occurs most often in the spleen, blood, and bone marrow. It has been associated with hepatitis C virus (HCV) infection.

For more information on disease diagnosis, please view the *Understanding Lymphoma and CLL Guide* on the Foundation's website (visit **lymphoma.org/publications**).

Treatment Options

When patients show no symptoms, doctors may decide to monitor the patient without treating the disease. This approach is called active surveillance, or *watchful waiting*. In this case, patients' overall health and disease are monitored through regular check-up visits that may include laboratory (like a complete blood cell count) and imaging tests (such as computed tomography [CT] scans). To know more about active surveillance, view the Active Surveillance fact sheet on the Lymphoma Research Foundation's website at **lymphoma.org/publication**.

Treatment is started if the patient begins to develop lymphoma-related symptoms or there are signs that the disease is progressing (cancer is growing and/or spreading). Treatment selection for a patient with MZL depends on:

- The MZL subtype, *stage* (the size of the cancer is and whether it has spread), and location (where in the body the tumor is located) of the MZL.
- Patient's age and overall health.
- MZL signs or symptoms.

Types of treatment for MZL include:

- Antibiotics (drugs that fight bacterial infections).
- Radiation therapy (uses high-energy radiation to kill cancer cells).
- *Immunotherapy* (drugs that use the body's immune system to fight cancer).
  - Monoclonal antibodies (proteins made in the laboratory that bind to cancer cells and help the immune system destroy them) such as rituximab (Rituxan).
  - Immunomodulatory drugs (drugs that work on the immune system directly by activating or slowing down the activity of specific proteins).
- *Chemoimmunotherapy* is a combination of *chemotherapy* (drugs that stop the growth of or kill cancer cells) with immunotherapy.
- Targeted therapies (drugs that target molecules that cancer cells use to grow and spread) such as Bruton's tyrosine kinase (BTK) inhibitors.
- Surgery.

Gastric MALT Lymphomas

Since gastric MALT lymphoma is often the result of an infection with *Helicobacter pylori*, the initial treatment combines therapy with two antibiotics and one *proton pump inhibitor* (PPI, drugs that reduce the amount of acid in the stomach), typically given for two weeks. PPIs help to prevent or heal stomach ulcers (sores on the walls of the stomach). In about 80% of cases, MALT lymphomas go away after antibiotic and PPI treatment, although this may take several months.

Most gastric MALT lymphomas are low-grade lesions that grow slowly and do not commonly spread to other places in the body. If the lymphoma relapses (returns after treatment) or becomes refractory (does not respond to treatment) after antibiotic therapy, there are many additional treatment options available. This includes another round of antibiotic treatment, radiation, and immunotherapy with monoclonal antibodies targeting CD20 such as rituximab (Rituxan), alone or in combination with chemotherapy (chemoimmunotherapy). Common initial chemoimmunotherapy regimens are:

- Bendamustine (Treanda) plus rituximab (BR).
- R-CHOP (rituximab [Rituxan], cyclophosphamide, doxorubicin, vincristine, and prednisone).
- R-CVP (rituximab [Rituxan], cyclophosphamide, vincristine, and prednisone).

Patients seeking information about immunotherapy should view the *Immunotherapy and Other Targeted Therapies* fact sheet on the Foundation's website (**lymphoma.org/publications**).

Non-Gastric MALT Lymphomas

Non-gastric MALT lymphomas can appear throughout the body. Therefore, treatment is usually based on the exact location of the lymphoma and how far it has spread. For ocular adnexa lymphoma (OAL), radiation therapy with or without antibiotic therapy is usually very effective, and patients may achieve *durable remission* (no signs or symptoms of disease for a long time). The antibiotic doxycycline has been shown to be effective in MALT that affects the area around the eye, especially in certain areas of the world where infection with *Chlamydia psittaci* is commonly associated with OAL. In localized cases, treatment usually includes radiation therapy. In rare cases, where radiation is not feasible, surgery can be used as an alternative.

More advanced disease is usually treated with immunotherapy such as the monoclonal antibody rituximab (Rituxan), with or without chemotherapy (as described above).

Nodal MZL

Because nodal MZL is most often a slow-growing disease, physicians may recommend an active surveillance or watchful waiting approach until symptoms appear. When treatment is necessary, options include radiation therapy, chemotherapy and/or immunotherapy, and other treatments commonly used in other types of slow-growing lymphomas, such as follicular lymphoma.

Splenic MZL

Treatment is not always immediately necessary for splenic MZL, but when a treatment is needed, several options exist. Some patients may receive a surgery called *splenectomy* (removal of the spleen) while other patients may be given rituximab (Rituxan) with or without chemotherapy. When the splenic MZL is associated with hepatitis C virus (HCV) infection, treatment of the infection might cure the lymphoma.

New treatments for all subtypes have been recently approved for relapsed disease. Lenalidomide (Revlimid), is an immunomodulatory oral (taken by mouth such as pills) medication that has been approved by the FDA for the treatment of patients with MZL who have received at least one prior therapy, and it is used in combination with rituximab (Rituxan), often referred to as *R*^{2} (R-squared). Recently, another BTK inhibitor called zanubrutinib (Brukinsa) was approval for use in adult patients with relapsed or refractory MZL after at least one prior anti-CD20-based regimen.

For all subtypes, biosimilar therapies (drugs that are similar to an existing biological therapy [reference drug] but may cost less than the reference drug) may be an option for patients who are taking rituximab. These include rituximab-abbs and rituximab-pvvr. For more information, patients should view the Biosimilars fact sheet on Lymphoma Research Foundation website at lymphoma.org/publications and talk to their physician.

Treatments Under Investigation

Many new treatments (also referred to as investigational drugs) and treatment combinations (two or more treatments given at the same time) are currently being tested in clinical trials for patients with newly diagnosed and relapsed or refractory MZL. Results from these clinical trials may improve or change the current standard of care (the proper treatment that is widely used by healthcare professionals and accepted by medical experts). **Table 1** (below) lists some of these investigational drugs that can be accessed through a clinical trial. For more information on clinical trials, view the *Understanding Clinical Trials* publication on the Lymphoma Research Foundation's website at **lymphoma.org/publication** (**Table 1**).

It is critical to remember that today's scientific research is always evolving. Treatment options may change as new treatments are discovered and current treatments are improved. Therefore, it is important that patients check with their physician or with the Foundation for any treatment updates that may have recently appeared. It is also very important that all patients consult with a specialist to clear up any questions.

Table 1: Investigational Drugs for Newly Diagnosed and Relapsed or Refractory Marginal Zone Lymphoma

Agent (drug)	Class (type of treatment)
Acalabrutinib (Calquence)	Targeted therapy; BTK inhibitor
Axicabtagene ciloleucel (Yescarta)	CAR T cell therapy; anti-CD19
Bortezomib (Velcade)	Targeted therapy; proteasome inhibitor
HMPL-689	Targeted therapy; PI3Kδ inhibitor
Idelalisib (Zydelig)	Targeted therapy; PI3Kδ inhibitor
Ixazomib (Ninlaro)	Targeted therapy; proteasome inhibitor
Mosunetuzumab (Lunsumio)	Immunotherapy; bispecific antibody
Nivolumab (Opdivo)	Immune checkpoint inhibitor; anti-PD-1 receptor
Obinutuzumab (Gazyva)	Immunotherapy; monoclonal antibody, anti-CD20
Parsaclisib (IBI376)	Targeted therapy; PI3Kδ inhibitor
Pembrolizumab (Keytruda)	Immune checkpoint inhibitor; anti-PD-1 receptor
Polatuzumab vedotin (Polivy)	Immunotherapy; antibody-drug conjugate
Tafasitamab (Monjuvi)	Immunotherapy; monoclonal antibody, anti-CD19
Venetoclax (Venclexta)	Targeted therapy; BCL2 inhibitor
Selinexor (Xpovio)	Targeted therapy; XPO1 inhibitor
BGB-10188	Targeted therapy; PI3Kδ inhibitor

BCL2, B-cell lymphoma 2 protein; BTK, Bruton tyrosine kinase; CAR, chimeric antigen receptor; CD, cluster of differentiate; PD-1, programmed cell death protein 1; PI3K, phosphoinositide 3-kinase; XPO1, exportin 1.

Clinical Trials

Clinical trials are crucial in identifying effective drugs and optimal treatment doses for patients with lymphoma. Patients interested in participating in a clinical trial should view the *Understanding Clinical Trials* fact sheet on the Foundation's website (**lymphoma.org/publications**), talk to their physician, or contact the Helpline for an individualized clinical trial search by calling **(800) 500-9976** or emailing **helpline@lymphoma.org**.

Follow-up

Patients with lymphoma should have regular visits to their physician. During these visits, medical tests (such as blood tests, computed tomography [CT] scans, and positron emission tomography [PET] scans) may be required to evaluate the need for additional treatment.

Some treatments can cause long-term (occur **during** treatment and continue for months or years) side effects or late side effects (appear only months, years or decades **after** treatment has ended). These side effects can vary depending on the following factors:

- Duration of treatment (how long the treatment lasted).
- Frequency of treatment (how often was the treatment was administered.
- Type of treatment given.
- Age and gender of the patient.
- Patient overall health at the time of their treatment.

A physician and their care team will check for these side effects during follow-up care. Visits may become less frequent the longer the patient stays in remission.

Patients and their care partners are encouraged to keep copies of all medical records. This includes test results as well as information on the type, amount, and duration of all treatments received. Medical records are important for keeping track of any side effects resulting from treatment or potential disease recurrences. The Foundation's award-winning *Focus On Lymphoma* mobile app can help patients manage this documentation.

Lymphoma Care Plan

Keeping your information in one location can help you feel more organized and in control. This also makes it easier to find information pertaining to your care and saves valuable time. The Foundation's Lymphoma Care Plan document organizes information on your health care team, treatment regimen, and follow-up care. You can also keep track of health screenings and any symptoms you experience to discuss with your health care provider during future appointments. The Lymphoma Care Plan document can be accessed by visiting **lymphoma.org/publications**.

Patient Education Programs

The Foundation also offers a variety of educational activities, including live meetings and webinars for individuals looking to learn directly from lymphoma experts. These programs provide the lymphoma community with important information about the diagnosis and treatment of lymphoma, as well as information about clinical trials, research advances and how to manage/cope with the disease. These programs are designed to meet the needs of a lymphoma patient from the point of diagnosis through long-term survivorship. To view our schedule of upcoming programs, please visit **lymphoma.org/programs**.

Helpline

The Foundation's Helpline staff are available to answer your general questions about lymphoma and treatment information, as well as provide individual support and referrals to you and your loved ones. Callers may request the services of a language interpreter. The Foundation also offers a one-to-one peer support program called the Lymphoma Support Network and clinical trials information through our Clinical Trials Information Service. For more information about any of these resources, visit our website at **lymphoma.org**, or contact the Helpline at **(800) 500-9976** or **helpline@lymphoma.org**.

Para información en Español, por favor visite **lymphoma.org/es**. (For Information in Spanish please visit **lymphoma.org/es**).

Focus on Lymphoma Mobile App

Focus on Lymphoma is the first app to provide patients and their care partners with tailored content based on lymphoma subtype, and actionable tools to better manage diagnosis and treatment. Comprehensive lymphoma management, conveniently in one secure and easy-to-navigate app, no matter where you are on the care continuum. Get the right information, first, with resources from the entire Lymphoma Research Foundation content library, use unique tracking and reminder tools, and connect with a community of specialists and patients. To learn more about this resource, visit our website at **lymphoma.org/mobileapp**, or contact the Foundation's Helpline at **(800) 500-9976** or **helpline@lymphoma.org**.

Lymphoma Research Foundation

Research. Community. Cure.

Helpline
(800) 500-9976
helpline@lymphoma.org

lymphoma.org
lymphoma@lymphoma.org

Stay Connected

The Lymphoma Research Foundation appreciates the expertise and review of our Editorial Committee:

Leo I. Gordon, MD, FACP
Co-Chair
Robert H. Lurie Comprehensive Cancer Center of Northwestern University

Kristie A. Blum, MD
Co-Chair
Emory University School of Medicine

Jennifer E. Amengual, MD
Columbia University

Carla Casulo, MD
University of Rochester Medical Center

Alex Herrera, MD
City of Hope

Shana Jacobs, MD
Children's National Hospital

Patrick Connor Johnson, MD
Massachusetts General Hospital

Manali Kamdar, MD
University of Colorado

Ryan C. Lynch, MD
University of Washington

Peter Martin, MD
Weill Cornell Medicine

Neha Mehta-Shah, MD, MSCI
Washington University School of Medicine in St. Louis

M. Lia Palomba, MD
Memorial Sloan Kettering Cancer Center

Pierluigi Porcu, MD
Thomas Jefferson University

Sarah Rutherford, MD
Weill Cornell Medicine

Supported through grants from:

Genentech, A Member of the Roche Group | Biogen | MERCK | AstraZeneca