

Understanding Lymphoma: Marginal Zone Lymphoma

Marginal zone lymphomas (MZLs) are a group of indolent (slow-growing) B-cell non-Hodgkin lymphomas (NHLs), beginning in a part of lymph tissue called the marginal zone, which account for approximately 5 to 10 percent of all NHL cases. The median age at diagnosis is 67 years, and they are slightly more common in men than in women.



TYPES OF MZL

Mucosa-associated lymphoid tissue (MALT) lymphoma or extranodal MZL is the most common form of MZL (61% of all MZL cases). MALT lymphomas usually arise in organs that are devoid of lymphoid tissue. MALT lymphomas are most commonly found in the stomach (called gastric MALT), but can also occur in other organs (called non-gastric MALT) like the small intestine, salivary glands, thyroid, breast, around the eye (ocular adnexa lymphoma [OAL]), lung and skin. Very frequently, MALT lymphomas arise secondary to chronic inflammation caused by infection (with bacteria or viruses) or autoimmune conditions (such as Hashimoto's thyroiditis or Sjogren's syndrome). Some of the microorganisms that have been shown to cause MALT lymphoma include chronic infection with *Helicobacter pylori*, which has been implicated in chronic inflammation of the stomach region causing gastritis. *Chlamydia psittaci* can cause orbital MALT lymphoma. **Mediterranean abdominal lymphoma**, also known as immunoproliferative small intestinal disease, is a type of MALT lymphoma that affects young adults in eastern Mediterranean countries. Most cases originate in the abdomen and occur in patients infected with *Campylobacter jejuni*.

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.



TREATMENT OPTIONS

Treatment selection for a patient with MZL depends on the type, stage, and location of the disease, the patient's age and overall health, and any lymphoma-related signs or symptoms.

GASTRIC MALT LYMPHOMAS

Since gastric MALT lymphoma is often the result of an infection with *Helicobacter pylori*, the initial treatment is a triple therapy of two antibiotics combined with proton pump inhibitors (PPIs),

typically given for two weeks. PPIs reduce the production of stomach acid to help prevent or heal ulcers. In about 90 percent of cases, these lymphomas go away following antibiotic and PPI treatment, although this may take several months. Most gastric MALT lymphomas are low-grade lesions that grow slowly and do not tend to spread to other places in the body. If the lymphoma *relapses* (disease returns after treatment) or becomes *refractory* (does not respond to treatment) after triple therapy, there are many additional treatment options available, including another round of antibiotic treatment, radiation, and monoclonal antibodies targeting CD20 such as rituximab (Rituxan), alone or in combination with chemotherapy.

NON-GASTRIC MALT LYMPHOMAS

Non-gastric MALT lymphomas can appear in a variety of areas throughout the body. Therefore, treatment is usually based on the exact location and extent of spread. For OAL, radiation therapy with or without antibiotic therapy usually has an excellent chance of response and patients can stay in remission for a long time. The antibiotic doxycycline has been shown to be effective in MZL that affects the area around the eye in certain areas of the world where infection with *Chlamydia psittaci* is commonly associated with OAL. Physicians may defer further treatment until symptoms appear, an approach called *active surveillance*, also known as *watchful waiting* (observation with no therapy given). With this strategy, patients' overall health and disease are monitored through regular checkup visits and various evaluating procedures, such as laboratory and imaging tests. Active treatment is started if the patient begins to develop lymphoma-related symptoms or there are signs that the disease is progressing. In localized cases, treatment typically 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. Common initial chemotherapy combination treatments are bendamustine (Treanda) plus rituximab (BR) or R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone), which are used to treat other slow-growing lymphomas such as follicular lymphoma.

NODAL MZL

Because nodal MZL is most often a slow-growing disease, physicians may adopt 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. When treatment is deemed appropriate, several options exist. Some patients may receive a *splenectomy* (surgical removal of the spleen) while other patients may be given rituximab (Rituxan) with or without chemotherapy. In some cases, because of the association of this type of lymphoma with HCV, treatment of the HCV infection might cure the lymphoma.

New treatments for all subtypes have been recently approved for relapsed disease. Ibrutinib (Imbruvica) was the first drug to be specifically approved by the U.S. Food and Drug Administration (FDA) for the treatment of MZL in these circumstances. It is used for the treatment of patients with MZL who require *systemic* (throughout the body) therapy and have received at least one prior anti-CD20-based therapy. Lenalidomide (Revlimid), is another oral 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 R2 (R-squared). Recently, the inhibitors umbralisib (Ukoniq) and zanubrutinib (Brukinsa) received 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 modeled after an existing biologic therapy) 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 (LRF) website at lymphoma.org/publications and talk to their physician.

TREATMENTS UNDER INVESTIGATION

Several new drugs and drug combinations are being studied in clinical trials for MZL and other slow-growing lymphomas, including:

- Acalabrutinib (Calquence)
- Axicabtagene ciloleucel (Yescarta)
- Bortezomib (Velcade)
- Copanlisib (Aliqopa)
- HMPL-689Idelalisib (Zydelig)
- Ixazomib (Ninlaro)
- Mosunetuzumab
- Nivolumab (Opdivo)
- Obinutuzumab (Gazyva)
- Panobinostat (Farydak)

- Parsaclisib (IBI376)
- Pembrolizumab (Keytruda)
- Polatuzumab vedotin (Polivy)
- Tafasitamab (Monjuvi)
- Ublituximab
- Venetoclax (Venclexta)
- Zandelisib (ME-401)

It is critical to remember that today's scientific research is continuously 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 LRF for any treatment updates that may have recently emerged.

CLINICAL TRIALS

Clinical trials are crucial in identifying effective drugs and determining optimal doses for patients with lymphoma. Patients interested in participating in a clinical trial should view the *Understanding Clinical Trials* fact sheet on LRF's website (lymphoma.org/publications), and the *Clinical Trials Search Request Form* at lymphoma.org, talk to their physician, or contact the LRF 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 with a physician who is familiar with their medical history and the treatments they have received. Medical tests (such as blood tests, computed tomography [CT] scans, and positron emission tomography [PET] scans) may be required at various times during remission to evaluate the need for additional treatment.

Some treatments can cause long-term side effects or late side effects, which can vary based on the duration and frequency of treatments, age, gender, and the overall health of each patient at the time of treatment. A physician will check for these side effects during follow-up care. Visits may become less frequent the longer the disease remains in remission.

Patients and their caregivers are encouraged to keep copies of all medical records and test results, as well as information on the types, amounts, and duration of all treatments received. This documentation will be important for keeping track of any side effects resulting from treatment or potential disease recurrences. LRF's award-winning *Focus On Lymphoma* mobile app (lymphoma.org/mobileapp) can help patients manage this documentation.



LRF'S HELPLINE AND LYMPHOMA SUPPORT NETWORK

A lymphoma diagnosis often triggers a range of feelings and concerns. In addition, cancer treatment can cause physical discomfort. The LRF Helpline staff members are available to answer your general questions about a lymphoma diagnosis 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. A part of the Helpline is LRF's one-to-one peer support programs, Lymphoma Support Network. This program connects patients and caregivers with volunteers who have experience with MZL, similar treatments, or challenges, for mutual emotional support and encouragement. Patients and loved ones may find this useful whether the patient is newly diagnosed, in treatment, or in remission.



MOBILE APP

Focus On Lymphoma is the first mobile application (app) that provides patients and caregivers comprehensive content based on their lymphoma subtype, including MZL, and tools to help manage their lymphoma such as, keep track of medications and blood work, track symptoms, and document treatment side effects. The *Focus On Lymphoma* mobile app is available for download for iOS and Android devices in the Apple App Store and Google Play. For additional information on the mobile app, visit **FocusOnLymphoma.org**. To learn more about any of these resources, visit our website at **lymphoma.org**, or contact the LRF Helpline at **800-500-9976** or **helpline@lymphoma.org**.



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. LRF offers a Lymphoma Care Plan as a resource for patients and their caregivers. LRF'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**.

Resources

LRF offers a wide range of free resources that address treatment options, the latest research advances, and ways to cope with all aspects of lymphoma and MZL. LRF also provides many educational activities, including our in-person meetings, podcasts, and webinars for people with lymphoma. For more information about any of these resources, visit our website at **www.lymphoma.org**, or contact the LRF 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**.)

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