

Marginal Zone Lymphoma

Overview

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

Marginal zone lymphomas (MZLs) are a group of *indolent* (slow-growing) B-cell NHLs, which account for approximately eight percent of all NHL cases. The average age at diagnosis is 60 years, and it is slightly more common in women than in men.

Types of MZL

Extranodal MZL or Mucosa-Associated Lymphoid Tissue (MALT) Lymphoma is the most common form of MZL, accounting for about two-thirds of all MZL cases per year and about five percent of all NHLs. This type occurs outside the lymph nodes in places such as the stomach, breast, small intestine, salivary gland, thyroid, structures around the eyes (ocular adnexa), and lungs. MALT lymphoma is divided into two categories: *gastric*, which develops in the stomach and is the most common site, and *non-gastric*, which develops outside of the stomach.

In many cases of MALT lymphoma, the patient has a previous medical history of chronic infection, inflammation, or autoimmune disorders at the affected organ. For example, *Helicobacter pylori* (*H. pylori*), a bacteria linked to chronic stomach irritation, has been associated with the vast majority of patients with gastric MALT lymphoma.

Nodal MZL occurs within the lymph nodes and accounts for about 31 percent of all MZL cases.

Splenic MZL occurs most often in the spleen, blood, and bone marrow. It has been associated with hepatitis C virus (HCV) infection. Splenic MZL comprises about eight percent of MZL cases diagnosed each year.

Treatment Options

Treatment selection for a patient with MZL depends on the type, the 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 *H. pylori*, the initial treatment is a triple therapy of two antibiotics combined with proton pump inhibitors (PPIs), which is 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* (returns after treatment) or becomes *refractory* (does not respond to treatment) after triple therapy, there are many additional treatment options available, including rituximab (Rituxan), radiation therapy, surgery, or ibrutinib (Imbruvica). Ibrutinib was the first therapy to be specifically approved by the U.S. Food and Drug Administration (FDA) for MZL. It was FDA-approved for the treatment of adult patients with MZL who require *systemic* (throughout the body) therapy and have received at least one prior anti-CD20-based therapy.

Non-Gastric MALT Lymphomas

Non-gastric MALT lymphoma can appear in a variety of areas throughout the body. Therefore, treatment is usually based on the exact location and extent of spread. Physicians may defer treatment until symptoms appear, an approach called *active surveillance* (also known as "watchful waiting" or "careful observation"). 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 based on testing during follow-up visits. When necessary, treatment typically includes surgery or radiation therapy. 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. The antibiotic doxycycline has been shown to be effective in MZL that affects the area around the eye (ocular adnexal lymphoma, OAL) in certain areas of the world where infection with *Chlamydia psittaci* is commonly associated with OAL. Ibrutinib (Imbruvica) may be used for systemic recurrences.

Nodal MZL

Because nodal MZL is most often a slow-growing disease, physicians may adopt an active surveillance 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. Ibrutinib (Imbruvica) may be used for relapsed MZL.

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); patients ineligible for surgery may receive low-dose radiation of the spleen. Other patients may be given rituximab (Rituxan) with or without chemotherapy or ibrutinib (Imbruvica). In some cases, because of the association of this type of lymphoma with HCV, interferon with or without antiviral therapy may be given to patients who show evidence of HCV infection.

Treatments Under Investigation

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

- Axicabtagene ciloleucel (Yescarta)
- Alisertib
- Bendamustine (Treanda)
- Blinatumomab (Blincyto)
- Bortezomib (Velcade)
- Buparlisib
- Carfilzomib (Kyprolis)
- Copanlisib (Aliqopa)
- Entospletinib
- Idelalisib (Zydelig)
- Ixazomib (Ninlaro)
- Lenalidomide (Revlimid)
- Nivolumab (Opdivo)
- Obinutuzumab (Gazyva)
- Panobinostat (Farydak)
- Pembrolizumab (Keytruda)
- Ublituximab
- Umbralisib
- Venetoclax (Venclexta)

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 Lymphoma Research Foundation (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 at lymphoma.org/publications, 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.

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.

Patient and Caregiver Support Services

A lymphoma diagnosis often triggers a range of feelings and concerns. In addition, cancer treatment can cause physical discomfort. LRF's *Lymphoma Support Network* 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 information useful whether the patient is newly diagnosed, in treatment, or in remission.

Resources

LRF offers a wide range of resources that address treatment options, the latest research advances, and ways to cope with all aspects of MZL, including our award-winning mobile app. LRF also provides many educational activities, from in-person meetings to teleconferences and webcasts for people with MZL, as well as patient guides and e-Updates that provide the latest disease-specific news and treatment options. To learn more about any of these resources, visit our websites at lymphoma.org/MZL or lymphoma.org, or contact the LRF Helpline at (800) 500-9976 or helpline@lymphoma.org.

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