LYMPHOMA RESEARCH • FOUNDATION

Getting the Facts

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Waldenström Macroglobulinemia

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).

Waldenström macroglobulinemia, which is a subtype of lymphoplasmacytic lymphoma, is a rare, *indolent* (slow-growing) B-cell lymphoma that occurs in less than two percent of patients with NHL. There are about 2,800 new cases of Waldenström macroglobulinemia diagnosed each year in the United States. The disease usually affects older adults and is primarily found in the bone marrow, although lymph nodes and the spleen may be involved. Lymphoma cells in the bone marrow grow and block normal cells, making it difficult for the bone marrow to produce normal amounts of red and white blood cells. This can result in *anemia* (low levels of red blood cells), *neutropenia* (low levels of white blood cells called neutrophils), and *thrombocytopenia* (low levels of platelets).

Patients with Waldenström macroglobulinemia have a high level of a protein called immunoglobulin M (IgM) in their blood. High levels of IgM can cause *hyperviscosity* (thickening of the blood). Although some patients experience no symptoms, when present, symptoms may include bleeding (particularly of the nose and gums), headaches, dizziness, double vision, tiredness, night sweats, pain or numbness in the extremities, and increased size of the liver, spleen, and lymph nodes.

To diagnose Waldenström macroglobulinemia, blood and urine tests are usually performed, as well as a bone marrow biopsy. During the biopsy, a needle is inserted into a bone (usually the pelvic bone), and a small sample of bone marrow is extracted for examination.

Treatment Options

Although Waldenström macroglobulinemia is an incurable disease, it is treatable, and many patients have a long-term response to treatment. For patients with no symptoms, physicians may decide not to treat the disease right away, an approach referred to as "watch and wait" or "watchful waiting." Watch and wait can last for many years for some patients. For patients who have symptoms, the type and severity of the symptoms (such as age, overall health, and the degree of thickness of the blood) help determine the type of treatment selected. Once treatment is deemed necessary, the choice of treatment is based on individual patient needs, as well as considerations for short-term and long-term side effects.

Some patients undergo a procedure called plasmapheresis to temporarily reverse or prevent the symptoms associated with the thickening of the blood. This procedure involves removing the patient's blood, passing it through a machine that removes the part of the blood containing the IgM antibody, and returning the remaining blood to the patient. Physicians often combine plasmapheresis with other more definitive treatments, such as chemotherapy.

In 2015, ibrutinib (Imbruvica) was the first therapy approved by the U.S. Food and Drug Administration (FDA) specifically for patients with Waldenström macroglobulinemia. There are many other drugs that can be used to manage this disease, alone and/or in various combinations, including the following:

- Bendamustine (Treanda)
- Bortezomib (Velcade)
- Chlorambucil (Leukeran)
- Cladribine (Leustatin)
- Fludarabine (Fludara)
- Rituximab (Rituxan)

Other agents used alone or in combination for primary treatment are cyclophosphamide (Cytoxan), carfilzomib (Kyprolis), and thalidomide (Thalomid).

For patients whose disease *relapses* (returns after treatment) or becomes *refractory* (does not respond to treatment), secondary therapies may be successful in providing additional remissions. Some of the previous therapies discussed can be used or reused depending on a patient's age, length of remission, stem cell transplant eligibility, and previous toxicities encountered. Additional therapies to treat relapsed/refractory Waldenström macroglobulinemia include:

- Everolimus (Afinitor)
- Ofatumumab (Arzerra) for patients who are intolerant to rituximab
- High-dose chemotherapy followed by an *autologous* (patients receive their own stem cells) or *allogeneic* (patients receive stem cells from a donor) stem cell transplant in select patients

Treatments Under Investigation

Several promising new drugs and drug combinations are being studied in clinical trials for the treatment of patients with Waldenström macroglobulinemia (some for relapsed/refractory disease), including:

- ACP-196
- ARGX-110
- Idelalisib (Zydelig)*
- IMO-8400
- Ixazomib (Ninlaro)
- Lenalidomide (Revlimid)
- Obinutuzumab (Gazyva)
- Panobinostat (Farydak)
- Venetoclax (Venclexta)

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Supported through grants from:

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Last Updated April 2016

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*As of April 2016, certain clinical trials, in the front-line setting using idelalisib in combination with another therapy, for patients with indolent NHL and chronic lymphocytic leukemia/small lymphocytic lymphoma were stopped to further evaluate increased adverse events that appeared to be the result of combining idelalisib with other cancer medicines. Further analysis is still needed, and patients should discuss options with their physician.

Chimeric antigen receptor-modified T-cell therapy targeting CD19 is another promising therapy for patients with Waldenström macroglobulinemia. In this technique, a patient's own T cells are removed and genetically reprogrammed to attack lymphoma cells. These clinical trials are in various phases of development. 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 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 and computed tomography [CT] scans) may be required at various times during remission to evaluate the need for additional treatment.

Some treatments can cause long-term effects or late effects, which can vary based on 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 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 effects resulting from treatment or potential disease recurrences.

Support

A lymphoma diagnosis often triggers a range of feelings and raises concerns. In addition, cancer treatment can cause physical discomfort. Support groups and online message boards can help patients connect with other people who have lymphoma. One-to-one peer support programs, such as the LRF Lymphoma Support Network, match lymphoma patients (or caregivers) with volunteers who have gone through similar experiences.

Resources

LRF offers a wide range of resources that address treatment options, the latest research advances, and ways to cope with all aspects of lymphoma, including our award-winning mobile app. LRF also provides many educational activities, from in-person meetings to teleconferences and webcasts, as well as disease-specific websites, videos, and eNewsletters for current lymphoma information and treatment options. To learn more 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.