LYMPHOMA RESEARCH • FOUNDATION

Understanding Transformed Lymphomas

The numerous types of non-Hodgkin lymphomas (NHLs) can be generally classified as being either *indolent* (slow-growing) or *aggressive* (fast-growing). Indolent lymphomas are generally not curable with standard therapy, but they are treatable. These are usually considered chronic diseases that may be successfully managed and may never become life-threatening in some patients.

Many patients with indolent lymphomas will not initially have symptoms or problems related to their disease. In these patients, studies have shown that beginning treatment at the time of diagnosis produces similar outcomes compared with waiting to begin treatment later, when symptoms develop. For this reason, patients with indolent lymphoma that is not causing symptoms or problems will often be followed with *active surveillance* also known as watchful waiting (observation with no treatment [drug therapy, radiation therapy, or stem cell transplantation] given). With this strategy, patients' overall health and disease are monitored through regular checkup visits and various evaluation procedures, such as laboratory and imaging tests.

Patients who are managed with active surveillance may not need treatment for many years, and some will never need treatment. Reasons to begin treatment of indolent lymphoma include *transformation* (large or rapidly growing), disease causing uncomfortable symptoms, or disease injuring the body's organs or decreasing healthy blood cells. Over the lifetime of a patient with an indolent lymphoma, the disease may need to be treated from time to time with one of the many effective treatments available, including immunotherapies and targeted therapies, chemotherapy, or radiation.

Transformed lymphoma occurs when an indolent lymphoma turns into a more aggressive one—for example, when follicular lymphoma transforms into diffuse large B-cell lymphoma (DLBCL) (see table). A transformation occurs when genetic changes in the indolent lymphoma cells cause them to begin growing faster and behaving more aggressively. Not all of the indolent lymphoma cells undergo transformation at once, so a patient with a transformed lymphoma will usually have a combination of indolent and aggressive ("transformed") lymphoma cells, which can be seen both clinically and under the microscope. The physician will choose a treatment that can work for both types of lymphoma, but the goal of treating the aggressive lymphoma is to *eradicate it* (get rid of it completely), because aggressive lymphoma that is not eradicated with treatment can become a life-threatening disease. The goal of treating an indolent lymphoma is to put it into *remission* (disappearance of signs and symptoms).

Certain risk factors increase the likelihood that an indolent lymphoma will transform. These risk factors include having *bulky disease* (a large tumor) or being in a high-risk group based on prognostic scoring systems such as the International Prognostic Index (IPI) and the Follicular Lymphoma International Prognostic Index (FLIPI). Still, among patients with an indolent lymphoma, the overall risk of developing a transformed lymphoma is low, with an average risk of one to three percent per year. The risk of developing a transformed lymphoma increases each year from the time of diagnosis until approximately 10 years afterwards, after which point transformations become rare. Over a lifetime, the total risk of transformation is approximately 20 percent, so the majority of patients with an indolent lymphoma will never develop a transformed lymphoma.

Many studies have shown that the risk of patients with indolent lymphoma progressing to transformed lymphoma was no different whether they were initially treated with chemotherapy or followed with observation.

FORMS OF LYMPHOMAS THAT TRANSFORM

INDOLENT LYMPHOMA	TRANSFORMED LYMPHOMA
Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL)	DLBCL (Richter syndrome); Hodgkin lymphoma (uncommon)
Follicular lymphoma (grades 1-2)	• Grade 3; greater proportion of large cells to small cells • DLBCL • High-grade lymphoma with MYC and BCL2 and/or BCL6 rearrangements
Lymphoplasmacytic lymphoma (Waldenström macroglobulinemia)	DLBCL
Mantle cell lymphoma (MCL)	Blastic (or blastoid) MCL
Marginal zone lymphoma (MZL)	DLBCL
Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL)	DLBCL

Treatment for transformed lymphoma depends on the clinical circumstances of the patient. Because these are aggressive diseases, aggressive treatment regimens with chemotherapy are usually used. Common chemotherapy regimens for transformed lymphoma include R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) or DA-EPOCH-R (dose-adjusted etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, and rituximab). If aggressive chemotherapy alone fails to induce remission, then *secondline* (treatment given when initial treatment does not work or stops working) treatments that may be considered include radioimmunotherapy and high-dose chemotherapy followed by stem cell transplantation. There is no single treatment for all patients with transformed lymphoma. The most appropriate treatment is selected for each patient based on the specific type of lymphoma, prior therapies received, age, presence of other medical problems, and general state of health.

Treatment options are changing as new therapeutics are becoming available, such as immunotherapies, targeted therapies and biosmiliars (drugs that are modeled after an existing biologic therapy) For more information on these types of therapies and other treatments for lymphoma visit lymphoma.org/publications. Because today's scientific research is continuously evolving, 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, 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) and the *Lymphoma Care Plan* (lymphoma.org/publications) 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. One-to-one peer support programs, such as LRF's Lymphoma Support Network, connect patients and caregivers with volunteers who have experience with lymphoma, 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 lymphoma, including our award-winning mobile app. LRF also provides many educational activities, from in-person meetings to webinars for people with transformed lymphoma, 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 website at lymphoma.org, or contact the LRF Helpline at (800) 500-9976 or helpline@lymphoma.org.

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