

Understanding Lymphoma: Transformed Lymphomas

The numerous types of non-Hodgkin lymphomas can be generally classified as being either *indolent (slow-growing)* or *aggressive (fast-growing)*. Indolent lymphomas are usually considered chronic diseases that may be successfully managed over years or decades in most 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.

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 1). Another example is Richter syndrome (also called Richter transformation), a rare condition where chronic lymphocytic leukemia/small lymphocytic lymphoma changes into a fast-growing type of lymphoma. 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 can become life-threatening. The goal of treating an indolent lymphoma is to put it into *remission* (disappearance of signs and symptoms).

Indolent Lymphoma	Transformed Lymphoma
Chronic lymphocytic leukemia/ small lymphocytic lymphoma	DLBCL (Richter syndrome); Hodgkin lymphoma (uncommon)
Follicular lymphoma (grades 1-2)	<ul style="list-style-type: none"> • DLBCL • High-grade lymphoma with MYC and BCL2 and/or BCL6 rearrangements (formerly known as double hit lymphoma)
Waldenström macroglobulinemia	DLBCL
Marginal zone lymphoma	DLBCL
Nodular lymphocyte-predominant Hodgkin lymphoma	DLBCL

Abbreviations: BCL2, B-cell lymphoma 2; BCL6, B-cell lymphoma 6; DLBCL, diffuse large B-cell lymphoma.

Certain risk factors increase the likelihood that an indolent lymphoma will transform. These risk factors include having *bulky disease* (a large tumor), higher grade of follicular lymphoma, 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 less than 10 percent for patients treated with rituximab, 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. However, the use of rituximab was associated with a lower risk of transformation.

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). Reduced-dose (mini) CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), R-GVCP (rituximab, gemcitabine, vincristine, cyclophosphamide, and prednisone) or R-CVP (rituximab, cyclophosphamide, vincristine, prednisone) may be used in older patients in whom full-dose chemotherapy would not be tolerable. In cases where an R-CHOP-like regimen was already used to treat the indolent lymphoma, treatment options may include immunochemotherapy or high-dose chemotherapy followed by stem-cell transplantation.

Patients with DLBCL arising from low-grade lymphoma may also be eligible for treatment with selinexor (Xpovio), tafasitamab-cxix (Monjuvi) or loncastuximab tesirine (Zynlonta). Emerging approaches like chimeric antigen receptor (CAR) T-cell therapies may also be an option. Axicabtagene ciloleucel (Yescarta), tisagenlecleucel (Kymriah), and lisocabtagene maraleucel (Breyanzi) are approved for patients with DLBCL arising from follicular lymphoma. 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 biosimilars (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 (visit 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.

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 transformed lymphoma, 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 transformed lymphoma, 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 transformed lymphoma. LRF also provides many educational activities, including our in-person meetings, 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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