

Understanding Lymphoma and Chronic Lymphocytic Leukemia (CLL) Transformed Lymphomas



The numerous types of non-Hodgkin lymphomas can be generally classified (grouped) as being either *indolent* (slow-growing) or *aggressive* (fast-growing). Indolent lymphomas are usually considered chronic diseases (conditions that can usually be controlled but not cured and require ongoing medical care) that may be successfully managed over years or decades in most patients.

Transformed lymphoma occurs when genetic mutations (permanent changes) in the DNA (deoxyribonucleic acid, the molecule that carries genetic information within the cell) in some indolent lymphoma cells cause them to grow faster and behave more aggressively (see Table 1). Not all of the indolent lymphoma cells undergo transformation at once. When examined under the microscope, biopsies (samples of lymph nodes) from patients with transformed lymphomas will usually have a combination of indolent and aggressive (“transformed”) lymphoma cells. If the number of fast-growing cells increases, the lymphoma can begin to behave more like an aggressive type (grows faster). Compared to indolent lymphomas, this transformed lymphoma usually requires more intensive types of treatment.

One example is Richter syndrome (also called Richter transformation), a rare condition where chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) changes into a fast-growing type of lymphoma.

The physician will choose a treatment that can work for both indolent and aggressive lymphomas, with the goal of eradicating the disease (get rid of it completely), because it can become life-threatening. DLBCL requires treatments that are more intensive and are given more urgently.

Table 1: Examples of Transformation

Indolent Lymphoma	Transformed Lymphoma
CLL/SLL	<ul style="list-style-type: none"> DLBCL (Richter syndrome) Hodgkin lymphoma (uncommon)
FL (grades 1-2) Grade 1-3A FL are low-grade (slow growing) lymphomas. Grade 3B is treated as high-grade (fast-growing) lymphoma.	<ul style="list-style-type: none"> DLBCL High-grade lymphoma with mutations in the MYC and BCL2 and/or BCL6 genes (a piece of DNA that contains information needed to produce the MYC and BCL2 proteins, respectively). This type is also known as double hit lymphoma.
WM	DLBCL
MZL	DLBCL
Nodular lymphocyte-predominant HL (also called nodular lymphocyte predominant B-cell lymphoma)	DLBCL

Abbreviations: BCL2, B-cell lymphoma 2; BCL6, B-cell lymphoma 6; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; HL, Hodgkin lymphoma; MYC, myelocytomatosis oncogene; MZL, marginal zone lymphoma; WM, waldenström macroglobulinemia.

Multiple risk factors associated with transformation have been identified. However, the presence of a risk factor does not mean that the lymphoma will transform. The risk factors for FL transformation include:

- Bulky disease (a large tumor).
- High grade FL.
- High-risk group based on prognostic scoring systems such as the International Prognostic Index (IPI) and the Follicular Lymphoma International Prognostic Index (FLIPI).

The overall risk of developing a transformed lymphoma is low among patients with an indolent disease, with an average risk of 2 to 3% per year that may stabilize (no longer increase) beyond 6 to 12 years after diagnosis. This means that the majority of these patients will never develop a transformed lymphoma. Many studies have shown that the risk of patients with indolent follicular lymphoma progressing to transformed lymphoma was no different whether they were initially treated with chemotherapy or followed with active surveillance (observation). However, the use of rituximab was associated with a lower risk of transformation. Over a lifetime, most patients with indolent lymphoma will not develop a transformed lymphoma.

For more information on diagnosis and disease staging, please view the *Understanding Lymphoma and CLL Guide* on the Foundation's website (visit lymphoma.org/publications).

Treatment Options

Treatment for transformed lymphoma usually includes aggressive chemotherapy regimens, which vary depending on the clinical condition (signs and symptoms of disease and overall health) of the patient.

The type of treatments for transformed lymphoma may include any of the following:

- *Chemotherapy* (drugs that stop the growth of or kill cancer cells).

- *Immunotherapy* (drugs that use the body's immune system to fight cancer):
 - Monoclonal antibodies (proteins made in the laboratory that bind to cancer cells and help the body fight cancer).
- Stem cell transplant (SCT, the patient is treated with high-dose chemotherapy or radiation to remove their blood-forming cells or stem cells, and then receives healthy stem cells to restore the immune system and the bone marrow's ability to make new blood cells).
- Targeted therapies (drugs that target molecules that cancer cells use to grow and spread).
- Chimeric antigen receptor (CAR) T cell therapies (a special type of immunotherapy that uses the patient's immune cells to fight cancer). Patients seeking more information about stem cell transplantation and/or CAR T-cell therapy should view the *Understanding Cellular Therapy* guide on the Foundation's website (lymphoma.org/publications).
- *Chemoimmunotherapy* (a combination of chemotherapy with immunotherapy):
 - A common approach is the combination of chemotherapy with a monoclonal antibody that targets CD20 (a protein at the surface of cancer cells), such as rituximab (Rituxan). Subcutaneous (given under the skin) rituximab (Rituxan Hycela) or rituximab biosimilars (like rituximab-abbs and rituximab-pvvr) are often used.
 - Biosimilars are drugs that are modeled after a biologic therapy that already exists. To learn more, please see the *Biosimilar Therapies* Factsheet on the Lymphoma Research Foundation's website at lymphoma.org/publications.

Some of the available treatment options that might be used if the patient has already received chemotherapy are described in the table below.

Table 2: Available Treatment Options for Transformed Lymphoma

Agents (Drugs)	Class of drug (type of treatment) and approved indication
Selinexor (Xpovio)	<ul style="list-style-type: none"> • Targeted therapy; XPO1 inhibitor. • Approved for patients with DLBCL arising from FL.
Tafasitamab-cxix (Monjuvi)	<ul style="list-style-type: none"> • Immunotherapy; anti-CD19 monoclonal antibody. • Approved for patients with DLBCL arising from low grade lymphoma.
Loncastuximab tesirine (Zynlonta)	<ul style="list-style-type: none"> • Immunotherapy; anti-CD 19 ADC. • DLBCL arising from low-grade lymphoma, and high-grade B-cell lymphoma.
Epcoritamab (Epkiny) Glofitamab (Columvi)	<ul style="list-style-type: none"> • Immunotherapy; Bispecific anti-CD20 antibodies. • DLBCL arising from indolent lymphoma.
Axicabtagene ciloleucel (Yescarta) Tisagenlecleucel (Kymriah) Lisocabtagene maraleucel (Breyanzi)	<ul style="list-style-type: none"> • CAR T-cell therapy • Approved for patients with DLBCL arising from FL.

Abbreviations: ADC, antibody-drug conjugate; CAR, chimeric antigen receptor; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; XPO1, blocking exportin 1.

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 (also called co-morbidities), and general state of health. Treatment options are changing as new drugs are becoming available, such as targeted therapy and immunotherapy drugs. Patients seeking information on these therapies should view the *Immunotherapy and Other Targeted Therapies* fact sheet on the Foundation's website (lymphoma.org/publications).

It is important to remember that scientific research is always improving. 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 Foundation for any treatment updates that may have recently appeared. It is also very important that patients consult with a specialist to clear up any questions.

Clinical Trials

Clinical trials are crucial in identifying effective drugs and the best doses for patients with lymphoma. Patients interested in participating in a clinical trial should view the *Understanding Clinical Trials* fact sheet on the Foundation's website (visit lymphoma.org/publications), and the Clinical Trials Search Request Form at lymphoma.org, talk to their physician, or contact the Foundation's 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 their physician. During these visits, medical tests (such as blood tests, computed tomography [CT] scans, positron emission tomography [PET] scans, and biopsies of suspicious masses or the bone marrow) may be required to evaluate the need for additional treatment. Some treatments can cause side effects that are long-term (occur during treatment and continue for months or years) or late side effects (appear only months, years or decades after treatment has ended). These side effects can vary depending on the following factors:

- Duration of treatment (how long was the treatment given).
- Frequency of treatment (how often was the treatment administered).
- Type of treatment given.
- Age and gender of the patient.
- Patient overall health 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 patient stays in remission.

Patients and their care partners are encouraged to keep copies of all medical records. These include test results as well as information on the types, amounts, and duration of all treatments received. Medical records are important for keeping track of any side effects resulting from treatment or potential disease recurrence. The Foundation's award-winning *Focus On Lymphoma* mobile app (lymphoma.org/mobileapp) and Lymphoma Care Plan (lymphoma.org/publications) can help patients manage this documentation.

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. The Foundation'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.

Patient Education Programs

The Foundation also offers a variety of educational activities, including live meetings and webinars for individuals looking to learn directly from lymphoma experts. These programs provide the lymphoma community with important information about the diagnosis and treatment of lymphoma, as well as information about clinical trials, research advances and how to manage/cope with the disease. These programs are designed to meet the needs of a lymphoma patient from the point of diagnosis through long-term survivorship. To view our schedule of upcoming programs, please visit lymphoma.org/programs.

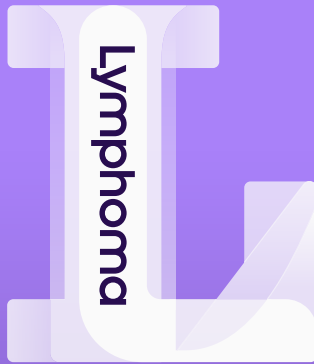
Helpline

The Foundation's Helpline staff are available to answer your general questions about lymphoma 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. The Foundation also offers a one-to-one peer support program called the Lymphoma Support Network and clinical trials information through our Clinical Trials Information Service. For more information about any of these resources, visit our website at lymphoma.org, or contact the 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).

Focus on Lymphoma Mobile App

Focus on Lymphoma is the first app to provide patients and their care partners with tailored content based on lymphoma subtype, and actionable tools to better manage diagnosis and treatment. Comprehensive lymphoma management, conveniently in one secure and easy-to-navigate app, no matter where you are on the care continuum. Get the right information, first, with resources from the entire Lymphoma Research Foundation content library, use unique tracking and reminder tools, and connect with a community of specialists and patients. To learn more about this resource, visit our website at lymphoma.org/mobileapp, or contact the Foundation's Helpline at (800) 500-9976 or helpline@lymphoma.org.



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