LYMPHOMA RESEARCH • FOUNDATION

Understanding Lymphoma: 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 an indolent lymphoma turns into a more aggressive one—for example, when follicular lymphoma (FL) transforms into diffuse large B-cell lymphoma (DLBCL) (see Table 1). In this case, slow-growing cells (FL cells) might be mixed with a few faster-growing cells (DLBCL cells). If the number of fast-growing cells increases, the lymphoma can begin to behave more like an aggressive type. This transformed lymphoma usually requires more-intensive types of treatment. Another example is Richter's syndrome (also called Richter's transformation), a rare condition where chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) changes into a fast-growing type of lymphoma. The transformation 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.

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.

The physician will choose a treatment that can work for both indolent and aggressive lymphomas, with the goal of eradicating it (getting rid of it completely), because it can become life-threatening. DLBCL requires treatment right away because of how aggressive it is.

Table 1. Examples of Transformation

Indolent Lymphoma	Transformed Lymphoma
CLL/SLL	• DLBCL (Richter's syndrome) • Hodgkin lymphoma (uncommon)
FL (grades 1-2) Grade 1A-3A FL are low-grade (slow-growing) lymphomas. Grade 3B is treated as high-grade (fast-growing) lymphoma.	• 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.

Certain risk factors increase the likelihood that an indolent lymphoma will transform, however, the presence of a risk factor does not mean that the lymphoma will transform.

These risk factors include:

- Bulky disease (a large tumor)
- High-grade FL
- High-risk grouping based on prognostic scoring systems such as the International Prognostic Index (IPI) and the Follicular Lymphoma International Prognostic Index (FLIPI). These scores evaluate how well the patient will do

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 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 (Rituxan) was associated with a lower risk of transformation. Over a lifetime, most patients with indolent lymphoma will not develop a transformed lymphoma.

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. Chemotherapy can be used alone or in combination with monoclonal antibodies (proteins made in the laboratory that bind to cancer cells and help the body fight cancer) that target CD20 (a protein at the surface of cancer cells), such as subcutaneous (given under the skin) rituximab (Rituxan Hycela) or rituximab biosimilars (like rituximab-abbs and rituximab-pvvr). Biosimilars are drugs that are modeled after a biologic therapy that already exists. To learn more, please see the *Understanding Lymphoma Biosimilar Therapies* fact sheet on the Lymphoma Research Foundation's (LRF's) website at **lymphoma.org/publications**.

Combining chemotherapy with monoclonal antibodies (chemoimmunotherapy) can increase the treatment response to chemotherapy. Common chemoimmunotherapy regimens for transformed lymphoma include:

- R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone)
- DA-EPOCH-R (dose-adjusted etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, and rituximab)
- R-GVCP (rituximab, gemcitabine, vincristine cyclophosphamide, and prednisolone)
- R-CVP (rituximab, cyclophosphamide, vincristine, prednisone) may be used in older patients in whom full-dose chemotherapy would not be tolerable

In some patients, high-dose chemotherapy followed by stem-cell transplantation (the patient is treated with high-dose chemotherapy 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) may also be an option. 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)	• Targeted therapy (drugs that target molecules that cancer cells use to grow and spread); XPO1 inhibitor • Approved for patients with DLBCL arising from FL
Tafasitamab-cxix (Monjuvi)	• Immunotherapy (treatment that uses the body's immune system to fight cancer); anti-CD19 monoclonal antibody • Approved for patients with DLBCL arising from low-grade lymphoma
Loncastuximab tesirine (Zynlonta)	• Immunotherapy; anti-CD19 ADC • DLBCL arising from low-grade lymphoma, and high-grade B-cell lymphoma
Axicabtagene ciloleucel (Yescarta)	• CAR T-cell therapy (a special type of immunotherapy that uses the patient's immune cells to fight cancer) • Approved for patients with DLBCL arising from FL
Tisagenlecleucel (Kymriah)	
Lisocabtagene maraleucel (Breyanzi)	

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

Patients seeking more information about stem cell transplantation and/or CAR T-cell therapy should view the *Understanding Cellular Therapy* guide on LRF's website (**lymphoma.org/publications**).

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 LRF'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 LRF 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 LRF's website (visit **lymphoma.org/publications**) and the *Clinical Trials Search Request Form* on **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 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 of 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 the treatment lasted)
- Frequency of treatment (how often the treatment was administered)
- Type of treatment given
- Age and gender of the patient
- Patient's 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 caregivers are encouraged to keep copies of all medical records. These include test results as well as information on the type, amount, and duration of all treatments received. Medical records are important for keeping track of any side effects resulting from treatment or potential disease recurrence. LRF'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 AND PATIENT EDUCATION PROGRAMS

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'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**. LRF also offers a variety of educational activities, including live meetings and webinars, for individuals looking to learn directly from lymphoma experts. To view our schedule of upcoming programs, please visit **lymphoma.org/programs**.

LRF Helpline

The LRF 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. LRF 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 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**).

LRF FOCUS ON LYMPHOMA MOBILE APP

Focus on Lymphoma is the first app to provide patients and their caregivers with tailored content based on lymphoma subtype and actionable tools to better manage diagnosis and treatment. It provides convenient and comprehensive lymphoma management 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 LRF Helpline at **800-500-9976** or **helpline@lymphoma.org**.

LRF appreciates the expertise and review of our Editorial Committee:

Leo I. Gordon, MD, FACP
Co-Chair
Robert H. Lurie Comprehensive Cancer Center of Northwestern University

Kristie A. Blum, MD
Co-Chair
Emory University School of Medicine

Jennifer E. Amengual, MD
Columbia University

Carla Casulo, MD
University of Rochester Medical Center

Alex Herrera, MD
City of Hope

Shana Jacobs, MD
Children's National Hospital

Patrick Connor Johnson, MD
Massachusetts General Hospital

Manali Kamdar, MD
University of Colorado

Ryan C. Lynch, MD
University of Washington

Peter Martin, MD
Weill Cornell Medicine

Neha Mehta-Shah, MD, MSCI
Washington University School of Medicine in St. Louis

M. Lia Palomba, MD
Memorial Sloan Kettering Cancer Center

Pierluigi Porcu, MD
Thomas Jefferson University

Sarah Rutherford, MD
Weill Cornell Medicine

Contact LRF:

Helpline: (800) 500-9976

Email: helpline@lymphoma.org

www.lymphoma.org

Supported through grants from: Bristol Myers Squibb · Genentech | Biogen

The *Understanding Lymphoma* fact sheet series is published by the Lymphoma Research Foundation (LRF) for the purpose of informing and educating readers. Facts and statistics were obtained using published information, including data from the Surveillance, Epidemiology, and End Results (SEER) Program. Because each person's body and response to treatment is different, no individual should self-diagnose or embark upon any course of medical treatment without first consulting with his or her physician. The medical reviewer, the medical reviewer's institution, and LRF are not responsible for the medical care or treatment of any individual.

© 2023 Lymphoma Research Foundation

Last updated 2023