Understanding Lymphoma and Chronic Lymphocytic Leukemia (CLL)

Oral Anticancer Agents and Adherence to Treatment in Lymphoma

Lymphoma Research Foundation

In the past, most treatments for lymphoma had to be given through a needle inserted directly into a vein (intravenously, IV) at a hospital or cancer center. However, today there are many anticancer drugs for the treatment of lymphoma that can be taken by mouth (also called oral agents), in tablet/capsule form.

Oral agents can be very effective at slowing down cancer cell growth and at maintaining long-term remission (disappearance of signs and symptoms). Although oral agents are pills that you can take at home, they can have side effects.

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

Oral Treatment Options

Oral anticancer agents include:

- Targeted therapies: Drugs directed against specific molecules that cancer cells use to survive and/or spread. Targeted therapies usually affect fewer normal cells when compared to chemotherapy, resulting in fewer serious side effects.
- Chemotherapy agents: Drugs directed against any rapidly dividing cell, both normal and tumor cells. Because chemotherapy agents cannot tell the difference between cancer cells and normal cells, they can also damage normal rapidly dividing cells such as those in the hair follicles, mouth, and blood. This can lead to side effects such as low blood cell counts, mouth sores, nausea, vomiting, diarrhea, or hair loss.
- Immunomodulatory agents: Drugs that activate or slow down the immune system and may also have antiangiogenic properties, which means they can prevent cancer cells from getting nutrients from the blood eventually causing their death.

United States Food and Drug Administration (FDA)-approved targeted and immunomodulatory agents are listed in **Table 1** and oral chemotherapy agents are listed in **Table 2** below. In the indications, the term "relapsed" refers to cancer that returns after treatment and "refractory" means that the cancer has not responded to treatment. Medication may be taken alone or in combination with other drugs, depending on the individual patient and factors such as age, type of lymphoma, and overall health.

Differences Between Oral Anticancer Medications and IV Treatment

Although oral anticancer medications may be just as effective as IV treatments, patients may need to receive oral therapy for years or even indefinitely, as opposed to the shorter duration (4-6 months) often used with IV treatments. Patients are monitored more closely in the early weeks and months after starting oral treatment, but after being on a medication for a longer period, they may only follow up every 2 to 4 months with their health care team. Bloodwork (measuring the amounts of blood cells and certain substances in a sample of blood) and tests may be done less frequently for patients on an oral agent compared with IV therapy. For these reasons, patients may feel less connected to their health care team than they would if receiving IV medications, and adherence (the ability to take all medications as prescribed) may be a challenge.

Because follow-up is often less frequent with oral therapies, side effects may also go unnoticed or unreported to the health care team, and patients may be uncertain about how to manage side effects on their own. Many of the side effects of oral medications can be managed with medication or lifestyle adjustments, therefore, patients should carefully track all side effects and report them to their health care team on a regular basis. It is also important to know that some side effects of oral agents may not appear in the early weeks to months after starting treatment. For example, patients taking ibrutinib (Imbruvica) and other drugs in the same class (Bruton's tyrosine kinase [BTK] inhibitors) may experience high blood pressure years after starting therapy. In addition, patients may not consider mild side effects important enough to report to their treatment team, but these can be uncomfortable over a long period and are often easily addressed with medication. It is important for patients to report all symptoms, mild or severe, to their treatment team.

Table 1: Oral Targeted and Immunomodulatory Agents for Lymphoma

Agent	Class	Indications
Acalabrutinib (Calquence)	Targeted therapy; BTK inhibitor	Approved for treatment of adult patients with CLL/SLL and MCL after at least one prior therapy
Bexarotene (Targretin)	Retinoid	Approved to treat skin problems arising from CTCL after at least one prior systemic therapy
Crizotinib (Xalkori)	Targeted therapy; tyrosine kinase receptor inhibitor	Approved for patients with 1 year of age and older and young adults with relapsed or refractory, systemic ALCL that is ALK-positive
Duvelisib (Copiktra)	Targeted therapy; PI3K delta, gamma inhibitor	Approved for treatment of adult patients with relapsed or refractory CLL/SLL after at least two prior therapies
Ibrutinib (Imbruvica)	Targeted therapy; BTK inhibitor	Approved for the treatment of adult patients with CLL/SLL with or without a 17p deletion, WM, MCL, MZL, and chronic graft vs host disease in adult and pediatric patients aged 1 year or older following allogeneic stem cell transplantation (stem cells from a donor) after failure of one or more systemic therapies
Idelalisib (Zydelig)	Targeted therapy; PI3K delta inhibitor	Approved for treatment of relapsed CLL in combination with rituximab (Rituxan), when rituximab alone would be considered appropriate therapy
Lenalidomide (Revlimid)	Immunomodulatory and antiangiogenic agent	Approved for relapsed or refractory MCL after two prior therapies including bortezomib (Velcade), and for previously treated FL or MZL in combination with a rituximab product
Pirtobrutinib (Jaypirca)	Targeted therapy; BTK inhibitor	Approved for adult patients with relapsed or refractory MCL after at least two lines of systemic therapy and CLL/SLL after at least two prior lines of therapy, including a BTK inhibitor and a BCL-2 inhibitor
Prednisone (Rayos)	Immunomodulatory and anti-inflammatory agent	Approved for palliative treatment of leukemias and lymphomas
Selinexor (Xpovio)	Targeted therapy; XPO1 inhibitor	Approved for treatment of adult patients with relapsed or refractory DLBCL, including DLBCL arising from follicular lymphoma, after at least 2 lines of systemic therapy
Tazemetostat (Tazverik)	Targeted therapy; EZH2 inhibitor	Approved for treatment of adult patients with relapsed or refractory FL with an EZH2 mutation after at least 2 prior systemic therapies or for adult patients with FL who have no satisfactory alternative treatment option
Venetoclax (Venclexta)	Targeted therapy; inhibitor of BCL2	Approved for treatment of adult patients with CLL/SLL
Vorinostat (Zolinza)	Targeted therapy; HDAC inhibitor	Approved for treatment of skin problems arising from CTCL in patients who have progressive, persistent, or recurrent disease on or following two prior therapies
Zanubrutinib (Brukinsa)	Targeted therapy; BTK inhibitor	Approved for the treatment of adult patients with MCL after at least one prior therapy, WM, and relapsed or refractory MZL who have received at least one anti-CD20-based regimen, CLL, and SLL

Abbreviations: ALCL, anaplastic large cell lymphoma; ALK, anaplastic lymphoma kinase; BCL-2, B-cell lymphoma-2; BTK, Bruton's tyrosine kinase; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; CTCL, cutaneous T-cell lymphoma; DLBCL, diffuse large B-cell lymphoma; EZH2, enhancer of zeste homolog 2; FL, follicular lymphoma; HDAC, histone deacetylase; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; PI3K, phosphoinositide 3-kinase; SLL, small lymphocytic lymphoma; XPO1, nuclear export receptor Exportin 1; WM, Waldenström macroglobulinemia.

Table 2: Chemotherapy Treatment Options: Oral Agents in Lymphoma

Agent	Class	Indications
Cyclophosphamide	Alkylating agent (mustard gas derivative)	Approved for HL, lymphocytic lymphoma, mixed-cell type lymphoma, histiocytic lymphoma, Burkitt's lymphoma, mycosis fungoides and leukemias
Chlorambucil (Leukeran)	Alkylating agent (nitrogen mustard)	Approved for CLL, lymphosarcoma, FL, and HL
Lomustine (Gleostine)	Alkylating agent (nitrosourea)	Approved for relapsed or refractory HL, used in combination therapy
Methotrexate	Antimetabolite	Approved for advanced mycosis fungoides and advanced-stage NHL
Procarbazine hydrochloride (Matulane)	Not defined, may act by inhibition of protein, RNA and DNA synthesis	Approved for combination therapy in stage III and IV HL

Abbreviations: CLL, chronic lymphocytic leukemia; DNA, deoxyribonucleic acid; FL, follicular lymphoma; HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma; RNA, ribonucleic acid.

Challenges with Adherence to Oral Anticancer Therapy

Oral agents are a convenient option for patients because they can be taken at home, which may be helpful for patients who have to travel a long distance to their treatment center. However, as patients are typically responsible for making sure they take their medication, there may be an increased risk of medication errors, like forgetting/skipping medications or changing the dosage, which can reduce the effectiveness and safety of the anticancer therapy. Taking all medications as prescribed to maximize the effectiveness of the treatment and to minimize serious side effects is critical.

Picking up oral anticancer medications from a pharmacy is often the responsibility of the patient, whereas IV therapy is provided at the patient's treatment center. Oral therapy is generally covered by comprehensive insurance plans, but filling prescriptions may be more challenging. Patients may be required to use selected pharmacies, and some pharmacies may not keep oral anticancer therapies on-site, which means patients must plan ahead to make sure that they have enough medication on hand.

Another consideration with oral anticancer therapy is how it may interact with other medicines taken by the patient. Pharmacists are often consulted to make sure that any medication the patient is already taking will not interact with the oral anticancer therapy. Drug interactions can decrease the effectiveness of oral anticancer therapy and/or increase the risk of side effects. The dose of some drugs may need to be adjusted and others may be replaced with a different medication that is less likely to interact with the oral anticancer therapy. Some antibiotics and antifungals may also interact with oral anticancer treatments and may be prescribed after the patient has been on oral anticancer therapy for some time.

Patients should never change the dosages of any prescribed medications and should always consult with their health care team before starting a new medication. In addition, foods and supplements may interact with oral anticancer therapies. For example, grapefruit juice is known to increase the blood levels of some drugs, and as a result, it may lead to toxicity (serious side effects associated with higher exposure to a drug).

Herbal remedies like St. John's wort can also change how well some anticancer drugs work and lead to serious side effects. Most supplements and herbal remedies are not regulated by the FDA, and whether or not they will interact with oral anticancer medications is often unknown. It is important for patients to consult with their physician before taking any supplements or herbal remedies.

One other consideration is that oral anticancer therapy can be expensive, especially when taken long-term. It is important for patients to discuss concerns regarding out-of-pocket costs with their treatment team. Programs exist to help cover the costs of medication, but these may not be available to all patients. If a patient's financial situation or insurance plan changes, and they are no longer able to pay for an oral anticancer medication (or supportive medication related to their cancer treatment), it is important for them to discuss it with their health care team.

Methods for Managing Oral Therapy and Adherence

Keeping track of medications and side effects can be complicated, particularly when a combination of medications with different dosing schedules are prescribed. For example, some oral anticancer medications are prescribed as one pill, once a day, and other medications taken as part of the same regimen may require multiple pills, multiple doses per day, or less frequent dosing. Getting into a regular routine early is important when starting oral therapy. Early follow-up by a pharmacist and/or other members of the health care team is often very helpful to make sure that patients have understood instructions and are correctly taking their medications. Continued watchfulness is important throughout treatment to make sure that changes in the patient's overall health or other medications that could affect treatment do not go unnoticed. During follow-ups, it is very important to report missed doses.

Missing a dose may affect test results, which should be considered when making decisions about the effectiveness of a treatment.

Keeping drug diaries can be helpful, as well as setting online reminders and using apps for smartphones and devices. Lymphoma Research Foundation's award-winning Focus On Lymphoma mobile app provides patients and care partners with comprehensive content based on their lymphoma subtype and tools to help manage the diagnosis and treatments, including a medication manager and side effects tracker. Users can access a full range of tools to help manage a patient's health care. The medication manager allows users to easily view all of their medications and track medicine schedules, including when to take oral anticancer therapy. Patients and care partners can also set reminders on their mobile devices and keep track of dosages and progress in the calendar. In addition, users can track the severity of side effects/symptoms as often as needed, to make reviewing progress with their health care team easier. Focus On Lymphoma is available for free download for iOS and Android devices in the Apple App Store and Google Play Store. For additional information on the mobile app, visit lymphoma.org/mobileapp.

Treatments Under Investigation

Some of the agents listed in the tables are being used in clinical trials for various types of lymphoma; some are used alone, and others are being added to existing therapy or used as part of new combination therapy regimens. The list of oral agents being tested in clinical trials is growing.

It is critical to remember that today's scientific research is always 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 Foundation for any treatment updates that may have recently emerged.

Clinical Trials

Clinical trials are crucial in identifying effective drugs and the best treatment 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 at **www.lymphoma.org/publications**, 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**.

Questions for Your Health Care Team

- Are there oral therapies for the subtype of lymphoma that I have?
- What is the goal of the oral medication for my lymphoma? Is it long-term disease control or achieving a complete remission so I can stop taking medication?
- Is combining oral therapy with chemotherapy to achieve remission an option for the subtype of lymphoma that I have?
- How long will I have to take oral medication for my lymphoma?
- How many medications will I be taking and how often?
- What are the benefits and potential risks of oral therapies for the subtype of lymphoma that I have?
  - Are the risks and benefits the same as other treatment options?
  - Will this treatment keep me from potentially receiving a different treatment in the future?
- Are there any activities, foods, or other medications that I should avoid while taking this treatment?
- What symptoms and side effects should I watch for, and what types of side effects would warrant a call or visit to my health care team?
- Are oral therapies for my lymphoma covered by insurance and is there a cost difference compared to other treatment options?
- What will my out-of-pocket costs be? How do the out-of-pocket costs compare to other treatment options? Are there resources to help me pay for my medications?
- What kinds of tools do you recommend to help me take my medication as prescribed?
- How often will I follow up with you and the health care team while I am taking this oral anticancer medication?

Table 3: Oral Treatments Under Investigation for Lymphoma

Agent	Class	Condition
Abexinostat (PCI-24781)	Targeted therapy; HDCA inhibitor	Under investigation for relapsed and refractory FL and DLBCL
Azacitidine (CC-486)	Chemotherapy; Antimetabolite	Under investigation for treatment of relapsed and refractory HL and AITL, DLBCL, and PTCL
BGB-11417 (Sonrotoclax)	Targeted therapy; BCL-2 inhibitor	Under investigation for CLL/SLL, WM, relapsed and refractory MCL
Golcadomide (CC-99282)	Targeted therapy; cereblon E3 ligase modulator	Under investigation for large B-cell lymphomas, and relapsed or refractory T-cell lymphomas
Lisaftoclax (APG-2575)	Targeted therapy; BCL-2 inhibitor	Under investigation for CLL/SLL
Nanatinostat (VRx-3996)	Targeted therapy; HDAC inhibitor	Under investigation for Epstein-Barr Virus associated Lymphoma
Tolinapant (ASTX660)	Targeted therapy; IAP antagonist	Under investigation for relapsed or refractory PTCL

Abbreviations: AITL, angioimmunoblastic T-cell lymphoma; BCL-2, B-cell lymphoma-2; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; HDAC, histone deacetylase; IAP, inhibitors of apoptosis proteins MCL, mantle cell lymphoma; PTCL, peripheral T-cell lymphoma; WM, Waldenström macroglobulinemia.

Follow-up

Patients with lymphoma should have regular visits with their physician. 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 (occur **during** treatment and continue for months or years) or late side effects (appear only months, years or decades **after** treatment has ended). These can depend 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.
- Patient age and gender.
- 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 disease remains in remission.

Patients and their care partners are encouraged to keep copies of all medical records. This includes 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 recurrences.

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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Supported through grants from:

Genentech, A Member of the Roche Group | Biogen | MERCK | AstraZeneca

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Last updated May 2024