

Understanding Oral Anticancer Adherence in Lymphoma

In the past, lymphoma treatment was mostly given intravenously (IV) at a hospital or cancer center. However, today there are many medications for the treatment of lymphoma that can be taken by mouth, either in liquid or tablet/capsule form.

Like IV anticancer medications, oral agents can be very effective at suppressing cancer growth and maintaining remission (disappearance of signs and symptoms). Although oral agents are pills that you can take at home, they can still have side effects.



ORAL TREATMENT OPTIONS

Oral anticancer agents include targeted therapies, chemotherapy agents, and immunomodulatory agents. Targeted therapies aim for specific molecules needed for cancer growth, which are often located within the cancer cell. Chemotherapy agents target any rapidly dividing cell, both normal and cancerous. Because chemotherapy agents cannot tell the difference between cancer cells and normal cells, they 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, and hair loss. In contrast, targeted therapies usually affect fewer normal cells, resulting in fewer of these types of side effects. Immunomodulatory agents stimulate or suppress the immune system and may also have antiangiogenic properties, which means they prevent cancer cells from getting nutrients from the blood.

U.S. Food and Drug Administration (FDA)-approved and investigational targeted and immunomodulatory agents for lymphoma are listed in **Table 1**. 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 does not respond to treatment. A medication may be taken alone or in combination with other medications, 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) with IV treatments. Patients are monitored 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 healthcare team. Blood work 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 healthcare 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 healthcare 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 of their treatment and report them to their healthcare 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 (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.

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, such as forgetting/skipping medications or self-adjusting 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 select pharmacies, and some pharmacies may not be equipped to prepare and store 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 drugs. 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 substituted 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 self-adjust dosages of any prescribed medications and should always consult with their healthcare 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 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 defray 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 healthcare 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 once weekly. Getting into a regular routine early is important when starting oral therapy. Early follow-up by a pharmacist and/or other members of the healthcare 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 labs and other aspects of a patient's exam, which should be considered when making decisions about the effectiveness of a treatment.

Drug diaries and medication dispensers that record when the pill container was opened can be helpful for tracking adherence. Online reminders and apps for smartphones and devices can also be useful. Lymphoma Research Foundation's (LRF's) award-winning *Focus On Lymphoma* mobile app provides patients and caregivers 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 suite of tools to help manage a patient's healthcare. The medication manager allows users to easily view all of their medications and track medicine schedules, including when to take an oral anticancer therapy. Patients and caregivers 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 healthcare team easier. *Focus On Lymphoma* is available for free download for iOS and Android devices in the Apple App Store and Google Play Store.



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 anticancer agents being tested in clinical trials is growing.

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

TABLE 1. ORAL TARGETED AND IMMUNOMODULATORY AGENTS FOR LYMPHOMA

AGENT	CLASS	INDICATIONS
Acalabrutinib (Calquence)	Targeted therapy; BTK inhibitor	Approved for treatment of CLL/SLL and for patients with 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 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 and FL after at least two prior therapies.
Ibrutinib (Imbruvica)	Targeted therapy; BTK inhibitor	Approved for treatment of adult patients with MCL after at least one prior treatment, CLL/SLL with or without a 17p deletion, MZL who require systemic therapy and after at least one prior anti-CD20-based therapy, and WM and chronic graft vs host disease following allogeneic stem cell transplantation (stem cells from a donor) after failure of one or more therapies
Idelalisib (Zydelig)	Targeted therapy; PI3K delta inhibitor	Approved for treatment of relapsed CLL in combination with rituximab, when rituximab alone would be considered appropriate therapy, and in relapsed FL or SLL after at least two prior therapies.
Lenalidomide (Revlimid)	Immunomodulatory and antiangiogenic agent	Approved for relapsed or refractory MCL after two prior therapies including bortezomib, and for previously treated FL or MZL in combination with rituximab
Prednisone (Rayos)	Immunomodulatory and anti-inflammatory agent	Approved for palliative treatment of leukemias and lymphomas
Selinexor (Xpovio)	Targeted therapy; XP01 inhibitor	Approved for treatment of 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 relapsed or refractory FL with an EZH2 mutation or for patients with FL who have no satisfactory alternative treatment option
Umbralisib (Ukoniq)	Targeted therapy; multiple kinase inhibitor (PI3K and CK1)	Approved for relapsed or refractory MZL after at least one prior anti-CD20-based regimen and relapsed or refractory FL after at least 3 prior lines of systemic therapy
Venetoclax (Venclexta)	Targeted therapy; inhibitor of B-cell lymphoma-2 (Bcl2)	Approved for treatment of CLL/SLL.
Vorinostat (Zolinza)	Targeted therapy; HDAC inhibitor	Approved for treatment of patients with CTCL who have progressive, persistent, or recurrent disease on or following two prior therapies.
Zanubrutinib (Brukinsa)	Targeted therapy; BTK inhibitor	Approved for the treatment of MCL after at least one prior therapy.

SELECTED AGENTS UNDER INVESTIGATION, IN PHASE 2/3 CLINICAL TRIALS

AGENT	CLASS	INDICATIONS
Abexinostat (PCI-24781)	Targeted therapy; HDCA inhibitor	Under investigation for HL, FL, DLBCL and MCL
APG-2575	Targeted therapy; Bcl-2 inhibitor	Under investigation for CLL/SLL
DTRM-555	Targeted therapy; BTK inhibitor	Under investigation for relapsed or refractory CLL/SLL, DLBCL and FL
Entospletinib (GS-9973)	Spleen tyrosine kinase inhibitor	Under investigation for treatment of CLL, FL, and other forms of NHL
Fimepinostat (CUDC-907)	Targeted therapy; dual PI3K and HDAC inhibitor	Under investigation for relapsed and refractory lymphoma. Granted FDA Fast Track designation for adult patients with relapsed or refractory DLBCL.
Iberdomide (CC-220)	Targeted therapy; cereblon E3 ligase	Under investigation for NHL, FL and DLBCL
LNS8801	Targeted therapy; GPER agonist	Under investigation for lymphoma (subtype not specified)
Nanatinostat (VRx-3996)	Targeted therapy; HDAC inhibitor	Under investigation for Epstein-Barr Virus associated Lymphoma
Panobinostat (Farydak)	Targeted therapy; HDAC inhibitor	Under investigation for patients with relapsed/refractory HL or NHL
Parsaclisib (INCB050465)	Targeted therapy; PI3K inhibitor	Under investigation for FL, MCL, relapsed or refractory DLBCL, CLL/SLL and NHL.
Tenalisib (RPG6530)	Targeted therapy; PI3K inhibitor	Under investigation for NHL and T cell lymphoma
Tolinapant (ASTX660)	Targeted therapy; IAP antagonist	Under investigation for relapsed or refractory PTCL, CTCL and ATLL
Zandelisib (ME-401)	Targeted therapy; PI3K inhibitor	Under investigation for NHL, FL and MZL

Abbreviations: ALCL, anaplastic large cell lymphoma; ALK, anaplastic lymphoma kinase; BTK, Bruton tyrosine kinase; CK, casein 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; FDA, food and drug administration; GPER, G protein-coupled estrogen receptor; FL, follicular lymphoma; HDAC, histone deacetylase; HL, hodgkin lymphoma; IAP, inhibitors of apoptosis proteins; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; NHL, non-Hodgkin lymphoma; PTCL, peripheral T cell lymphoma; PI3K, phosphoinositide 3-kinase; SLL, small lymphocytic lymphoma; WM, Waldenström macroglobulinemia; XPO1, nuclear export receptor Exportin 1.

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, MM, 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
Azacitidine (CC-486)	Antimetabolite	Under investigation for treatment of DLBCL, FL and AITL

Abbreviations: AITL, angioimmunoblastic T-cell lymphoma; CLL, chronic lymphocytic leukemia; DNA, deoxyribonucleic acid; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; HL, hodgkin lymphoma; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; RNA, ribonucleic acid.

QUESTIONS FOR YOUR HEALTHCARE 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 and 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 healthcare 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?
- 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 healthcare team while I am taking this oral anticancer medication?

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.

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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 lymphomas, similar treatments, or challenges, for mutual emotional support and encouragement. You may find this useful whether you or a loved one 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 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.

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 CLL/SLL including our award-winning mobile app. LRF also provides many educational activities, including our in-person meetings, podcasts, webinars for people with 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 www.lymphoma.org, or contact the LRF Helpline at (800) 500-9976 or helpline@lymphoma.org.

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