

# 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, maintaining remission (disappearance of signs and symptoms). Although oral agents are pills that you can take at home, they can have side effects.

## ORAL TREATMENT OPTIONS

Oral anticancer agents include targeted therapies, immunomodulatory agents, and chemotherapy agents. *Targeted therapies* aim for specific molecules needed for cancer growth which are often located within the cancer cell. *Chemotherapy agents* aim for 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 the immune system to destroy cancer cells 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** and oral chemotherapy agents are listed in **Table 2** (page 3). 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, IV treatments are often given over a period of 4 to 6 months, while patients may need to take oral therapy indefinitely (for years). Patients are typically monitored closely in the early weeks and months after starting oral treatment, but after being on a medication for a longer period of time, 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 they were receiving IV medications at a cancer treatment center, and *adherence*, which refers to a patient's ability to consistently take all medication as prescribed, may be a challenge for some patients.

Because follow-up is often less frequent with oral therapies compared with IV treatments, side effects of oral therapies 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, so patients should carefully track all side effects of their treatment and report them to their healthcare team on a regular basis so they can receive the best care. It is also important to know that some side effects of oral agents may not show up in the early weeks to months after starting treatment. For example, patients taking ibrutinib (Imbruvica) and other drugs in the same class (Bcr tyrosine kinase [BTK] inhibitors) may experience high blood pressure and swelling in their lower legs years after starting therapy. In addition, patients may not consider mild side effects important enough to report to their treatment team, but these mild side effects can often be uncomfortable over a long period of time 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 mistakes, such as forgetting/skipping medications

or self-adjusting the dosage, which can reduce the effectiveness 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 before starting an oral treatment to make sure that any medication the patient is already taking will not interact with the anticancer therapy. 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 drug interactions can decrease the effectiveness of the oral anticancer therapy and others can increase the risk of side effects. 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 than expected exposure to a drug). Most supplements and herbal remedies are not regulated by the FDA, and, therefore, whether they will interact with oral anticancer medications is not known. 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 tell 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 are prescribed, each with different dosing schedules. 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 are available and 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
Duvelisib (Copiktra)	Targeted therapy; phosphoinositide 3 kinase delta, gamma inhibitor	Approved for CLL/SLL and FL after at least two prior therapies. Under investigation for T-cell lymphomas
Ibrutinib (Imbruvica)	Targeted therapy; BTK inhibitor	Approved for treatment of patients with MCL after at least one prior treatment, CLL/SLL with or without a 17p deletion, MZL with 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; phosphoinositide 3 kinase delta inhibitor	Approved for treatment of relapsed (disease returns after treatment) CLL in combination with rituximab (Rituxan), and in relapsed FL or SLL after at least two prior therapies
Lenalidomide (Revlimid)	Immunomodulatory and antiangiogenic agent	Approved for relapsed/refractory (disease does not respond to treatment) MCL after two prior therapies including bortezomib (Velcade), and for previously treated FL or MZL in combination with a rituximab product. This regimen is known as R <sup>2</sup>
Selinexor (Xpovio)	Targeted therapy; XPO1 inhibitor	Approved for treatment of relapsed or refractory DLBCL not otherwise specified, including DLBCL arising from follicular lymphoma, after at least 2 lines of systemic therapy
Tazemetostat	Targeted therapy; EZH2 inhibitor	Approved for treatment of relapsed/refractory FL with an EZH2 mutation or for patients with relapsed/refractory FL who have no satisfactory alternative treatment option
Venetoclax (Venclexta)	Targeted therapy; inhibitor of B-cell lymphoma-2 (Bcl2)	Approved for treatment of CLL/SLL. Under investigation for patients with other types of B-cell NHL
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. Under investigation in patients with B-cell NHL and CLL
Zanubrutinib (Brukinsa)	Targeted therapy; BTK inhibitor	Approved for the treatment of MCL after at least one prior therapy. Under investigation for CLL/SLL, FL, MZL, and DLBCL

**TABLE 2. ELECTED AGENTS UNDER INVESTIGATION, IN PHASE 2-3 CLINICAL TRIALS**

AGENT	CLASS	INDICATIONS
Entospletinib (GS-9973)	Spleen tyrosine kinase inhibitor	Under investigation for treatment of CLL, FL, and other forms of NHL
Panobinostat (Farydak)	Targeted therapy; HDAC inhibitor	Under investigation for patients with relapsed/refractory HL or NHL
Spebrutinib (AVL-292; CC-292)	Targeted therapy; BTK inhibitor	Under investigation for patients with CLL/SLL, DLBCL, WM, and other forms of relapsed/refractory B-cell NHL
Umbralisib (TGR-1202)	Targeted therapy; phosphoinositide 3 kinase delta inhibitor	Under investigation for HL and B-cell NHL, including CLL and WM

Abbreviations: BTK, Bruton tyrosine kinase; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; CTCL, cutaneous T-cell lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; HDAC, histone deacetylase; HL, Hodgkin lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; NHL, non-Hodgkin lymphoma; SLL, small lymphocytic lymphoma; WM, Waldenström macroglobulinemia.

## ? 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 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?

## 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 disease 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 [lymphoma.org/mobileapp](http://lymphoma.org/mobileapp).

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## SUPPORT SERVICES

### LYMPHOMA SUPPORT NETWORK

A lymphoma diagnosis often triggers a range of feelings and concerns. In addition, cancer treatment can cause physical discomfort. One-to-one peer support programs, such as LRF's *Lymphoma Support Network*, 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.

### CLINICAL TRIALS INFORMATION SERVICE

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 and the *Clinical Trials Search Request Form* on LRF's website at [lymphoma.org/clinicaltrials](http://lymphoma.org/clinicaltrials), 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](mailto:helpline@lymphoma.org).

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.

### Resources

LRF offers a wide range of 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, from in-person meetings, webinars and podcasts 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 [lymphoma.org](http://lymphoma.org) or contact the LRF Helpline at (800) 500-9976 or [helpline@lymphoma.org](mailto:helpline@lymphoma.org).

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