

Understanding Oral Agents in Lymphoma

In the past, most treatments for lymphoma had to be given intravenously (IV) at a hospital or cancer center. However, today there are many chemotherapeutic drugs and targeted anticancer drugs for the treatment of lymphoma that can be taken by mouth, either in liquid or tablet/capsule form. Oral agents can be very effective at suppressing 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.

Oral agents may be beneficial for patients who have to travel a long distance to their treatment center since they can be taken at home. However, as patients are typically responsible for ensuring they take their pills, there may be an increased risk of medication errors, such as forgetting/skipping pills or self-adjusting the dosage, which can reduce the effectiveness of the anticancer therapy. Taking all medications as prescribed is important to maximize the effectiveness of the treatment and to minimize serious side effects.

Patients are typically monitored closely in the early weeks and months after starting an oral agent, but after being on a medication for a longer period of time, they may follow up with their healthcare team only every two to four months. Blood work and tests may be obtained 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, where they would have more frequent interaction with the healthcare staff. Side effects of oral anticancer 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.

MEDICATION TRACKING

Keeping track of medications and side effects can be complicated, particularly when medications prescribed have different dosing schedules. Drug diaries are available that can be helpful, as well as online reminders and apps for smartphones and devices. To assist with this, the 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 their diagnosis, 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 cancer 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 physician or nurse easier. *Focus On Lymphoma* is available for free 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.

ORAL TREATMENT OPTIONS

Oral agents include targeted therapies, immunomodulatory drugs, and chemotherapy agents. Targeted therapies are directed against specific molecules needed for tumor growth, whereas standard chemotherapy agents are directed against any rapidly dividing cell, both normal and tumor cells. Because chemotherapy agents do not distinguish between cancer cells and normal cells, they also damage normal rapidly dividing cells like those in the hair follicles, mouth, and blood. This leads 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 serious 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.

United States Food and Drug Administration (FDA) approved and investigational oral chemotherapy agents are listed in **Table 1** on the next page. Targeted and *immunomodulatory agents* (drugs that cause tumor cells to die, help keep tumors from getting nutrients from the blood, and stimulate the immune system to destroy cancer cells) for lymphoma are listed in **Table 2**.

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.

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.

CLINICAL TRIALS

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 on LRF's website at www.lymphoma.org/publications, 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.

TABLE 1. CHEMOTHERAPY TREATMENT OPTIONS: ORAL AGENTS IN LYMPHOMA

AGENT	CLASS	INDICATIONS
Cyclophosphamide (Cytoxan)	Alkylating agent (mustard gas derivative)	Used for Burkitt lymphoma, CLL, HL, NHL, mycosis fungoides, and as part of conditioning regimens for stem cell transplantation
Etoposide (Vepesid)	Topoisomerase II inhibitor	Used for NHL and CTCL
Chlorambucil (Leukeran)	Alkylating agent (nitrogen mustard)	Approved for CLL, follicular lymphoma, and HL. It is being studied in other NHL subtypes
Methotrexate (Rheumatrex)	Antimetabolite	Used for advanced mycosis fungoides (CTCL) and advanced-stage NHL
Azacitidine (CC-486)	Antimetabolite	Under investigation for treatment of DLBCL and AITL

Abbreviations: AITL, angioimmunoblastic T-cell lymphoma; CLL, chronic lymphocytic leukemia; CTCL, cutaneous T-cell lymphomas; DLBCL, diffuse large B-cell lymphoma; HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma.

TABLE 2. ORAL TARGETED AND IMMUNOMODULATORY AGENTS FOR LYMPHOMA

FDA-APPROVED AGENTS

AGENT	CLASS	INDICATIONS
Acalabrutinib (Calquence)	Targeted therapy; BTK inhibitor	Approved for treatment of patients with MCL after at least one prior therapy and for CLL/SLL. Under investigation for other forms of NHL
Bexarotene (Targretin)	Retinoid	Approved to treat skin problems arising from CTCL after at least one prior systemic 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 with 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
Idelalisib (Zydelig)	Targeted therapy; phosphoinositide 3-kinase delta inhibitor	Approved for treatment of relapsed (disease returns after treatment) CLL in combination with rituximab (Rituxan), or when rituximab alone would be considered appropriate therapy, and in relapsed FL or SLL in patients who have received at least two prior systemic 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 ²
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 systemic (spread throughout the entire body) 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
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, chronic lymphocytic leukemia; CTCL, cutaneous T-cell lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; HL, Hodgkin 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.

FOLLOW-UP

Patients with lymphoma should have regular visits with a physician who is familiar with their medical history and the treatments they have received. 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 or late side effects, which can vary based on the duration and frequency of treatments, age, gender, and the overall health of each patient 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 caregivers are encouraged to keep copies of all medical records and test results as well as information on the types, amounts, and duration of all treatments received. This documentation will be important for keeping track of any side effects resulting from treatment or potential disease recurrences.

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 www.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.

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LRF HELPLINE

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.

PATIENT EDUCATION

LRF offers a wide range of opportunities to learn about lymphoma.

Ask the Doctor About Lymphoma is a national series of two-hour, topic-specific, community-based programs that combine a presentation by a medical doctor with an extensive question-and-answer session.

Lymphoma Workshops are regional, full-day educational programs that provide the latest information about lymphoma, current treatment options, and patient support issues.

The North American Educational Forum on Lymphoma is held annually and provides critical information on treatment options, patient support issues, and the latest in lymphoma research.

Webinars are available on specific types of lymphoma, treatment options, and support topics.

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 to teleconferences and webcasts 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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