

Oral Agents in Lymphoma

Overview

Lymphoma is the most common blood cancer. The two main forms of lymphoma are Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). Lymphoma occurs when cells of the immune system called lymphocytes, a type of white blood cell, grow and multiply uncontrollably. Cancerous lymphocytes can travel to many parts of the body, including the lymph nodes, spleen, bone marrow, blood, or other organs, and form a mass called a tumor. The body has two main types of lymphocytes that can develop into lymphomas: B lymphocytes (B cells) and T lymphocytes (T cells).

In the past, most chemotherapy agents 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 are just as effective as IV anticancer drugs, and they also have similar side effects.

Oral agents are a convenient option for patients because 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 compromise the effectiveness of the anticancer therapy. It is critical that patients take all medications as prescribed to maximize the effectiveness of the treatment and to minimize toxicity and negative therapeutic outcomes. Since keeping track of medications can be complicated, particularly when a combination medication regimen is prescribed in which agents may 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.

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 direct interaction with the healthcare staff; however, taking oral agents at home may be beneficial for patients who have to travel a long distance to their treatment center. 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 alleviated by supportive care, 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.

Some oral agents are targeted therapies. 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.

FDA-approved and investigational oral 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 encourage the destruction of cancer cells) for lymphoma are listed in Table 1 on the next page.

Treatments Under Investigation

Some of the agents listed in Table 2 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 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.

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 | How it Works | Indications |
|----------------------------|-------------------------------------------|-------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------|
| Cyclophosphamide (Cytoxan) | Alkylating agent (mustard gas derivative) | Chemically modifies DNA to cause death of growing cells | Used for Burkitt lymphoma, CLL, HL, NHL, mycosis fungoides, and as part of conditioning regimens for stem cell transplantation |
| Etoposide (Vepesid) | Topoisomerase II inhibitor | Interferes with topoisomerase enzymes that control manipulation of the structure of DNA necessary for replication | Used for NHL and CTCL |
| Chlorambucil (Leukeran) | Alkylating agent (nitrogen mustard) | Chemically modifies DNA to cause death of growing cells | Approved for CLL, follicular lymphoma, and HL. It is being studied in other NHL subtypes |
| Methotrexate (Rheumatrex) | Antimetabolite | Interferes with DNA synthesis and cell growth | Used for advanced mycosis fungoides (CTCL) and advanced-stage NHL |

Abbreviations: CLL, chronic lymphocytic leukemia; CTCL, cutaneous T-cell lymphomas; HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma.

Table 2. Oral Targeted and Immunomodulatory Agents for Lymphoma

| FDA-Approved Agents | | | |
|------------------------|-------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Agent | Class | How it Works | Indications |
| Bexarotene (Targretin) | Retinoid | Selectively binds and activates retinoid X receptors, resulting in expression of genes that control cell growth and replication | Approved to treat skin problems arising from CTCL after at least one prior systemic therapy |
| Ibrutinib (Imbruvica) | Targeted therapy; BTK inhibitor | Inhibits B-cell receptor signaling needed for tumor cell survival and replication | 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 | Inhibits B-cell receptor signaling needed for tumor cell survival and replication | Approved for treatment of <i>relapsed</i> (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 |

Abbreviations: BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; CTCL, cutaneous T-cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; SLL, small lymphocytic lymphoma; WM, Waldenström macroglobulinemia.

Table 2. Oral Targeted and Immunomodulatory Agents for Lymphoma (continued)

| FDA-Approved Agents (continued) | | | |
|-----------------------------------------------------------------------------|--------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Agent | Class | How it Works | Indications |
| Lenalidomide (Revlimid) | Immunomodulatory and antiangiogenic agent | Delays growth of new blood vessels (angiogenesis) in tumors, boosts the immune system, and decreases chemicals, called cytokines, surrounding the tumor that tell it to grow | Approved for relapsed/refractory (disease does not respond to treatment) MCL after two prior therapies including bortezomib (Velcade) |
| Umbralisib (TGR-1202) | Targeted therapy; phosphoinositide 3-kinase delta inhibitor | Inhibits B-cell receptor signaling needed for tumor cell survival and replication | Under investigation for B-cell malignancies, including CLL |
| Venetoclax (Venclexta) | Targeted therapy; inhibitor of B-cell lymphoma-2 (<i>Bcl2</i>) | Targets proteins thought to prevent cancer cells from dying | Approved for treatment of previously treated (relapsed/refractory) patients with CLL who have a 17p deletion Under investigation for patients with other types of B-cell NHL |
| Vorinostat (Zolinza) | Targeted therapy; HDAC inhibitor | Inhibits HDAC enzymes needed for expression of genes in DNA to inhibit cancer cell growth and division | 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 |
| Selected Agents Under Investigation, in Phase II–III Clinical Trials | | | |
| Acalabrutinib (ACP-196) | Targeted therapy; BTK inhibitor | Inhibits B-cell receptor signaling needed for tumor cell survival and replication | Under investigation for CLL/SLL, MCL, and other forms of NHL |
| Duvelisib (IPI-145) | Targeted therapy; phosphoinositide 3-kinase delta, gamma inhibitor | Inhibits B-cell receptor signaling needed for tumor cell survival and replication | Under investigation for T-cell lymphomas and CLL/SLL |
| Entospletinib (GS-9973) | Spleen tyrosine kinase inhibitor | Interferes with B-cell signaling | Under investigation for treatment of CLL, FL, and other forms of NHL |
| Panobinostat (Farydak) | Targeted therapy; HDAC inhibitor | Inhibits HDAC enzymes needed for expression of genes in DNA to inhibit cancer cell growth and division | Under investigation for patients with relapsed/refractory HL or NHL |
| Spebrutinib (AVL-292; CC-292) | Targeted therapy; BTK inhibitor | Inhibits B-cell receptor pathway needed for tumor cell survival and replication | 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 | Inhibits B-cell receptor signaling needed for tumor cell survival and replication | Under investigation for B-cell malignancies, including CLL |

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; 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* (disappearance of signs and symptoms) 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.

Patient and Caregiver Support Services

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 lymphoma or chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), similar treatments, or challenges, for mutual emotional support and encouragement. Patients and loved ones may find this useful whether the patient is newly diagnosed, in treatment, or in remission.

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.

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

Teleconferences are hour-long, interactive telephone programs that provide an opportunity to learn more about lymphoma, treatments, and promising research from leading lymphoma experts.

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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