

Biologic and Novel Therapies in Lymphoma

Biologic therapy, also called biological response modifier therapy, works with the body's normal cell functions to fight cancer. The action of these therapies is more focused on specific targets, whereas conventional chemotherapy generally kills any rapidly dividing cell in the body. The term "biologics" refers to complex molecules that are created inside living cells in a laboratory (for example, bacteria, yeast cells, or purified mammalian cells). Biologic agents are often used in combination with chemotherapy regimens. Specific agents are used to target particular characteristics of cancer cells. Each biologic agent is only effective if a patient's cancer cells have the necessary target (for example, a specific protein) on the surface of the cell.

Immunotherapy

Monoclonal Antibodies

Monoclonal antibodies are the most common biologic agents used for lymphoma treatment. Antibodies produced by our immune system recognize and destroy "foreign" invaders such as bacteria and viruses. Scientists can now produce monoclonal antibodies in the laboratory that are designed to recognize *antigens* (specific molecules) that are present on the surface of certain cancer cells. Once in the bloodstream, monoclonal antibodies travel throughout the body and attach themselves to their specific target antigens.

Monoclonal antibodies can be given as *naked* (without any chemical modification) or *conjugated* (bound to a chemotherapy drug, radioactive particle, or toxin). Naked antibodies work by stopping or slowing the growth of tumor cells or by making it easier for the patient's immune system to recognize and destroy the tumor cell. Conjugated antibodies bring with them a medication, a *radioactive* (giving off radiation) particle, or a toxic chemical. When the antibody attaches to its target on the cancer cell, the toxic agent that is bound to it can then kill that cell. Some of the monoclonal antibodies' targets can be found on normal cells as well as the *malignant* (cancerous) cells. If a target is on normal cells, the normal cells can also be harmed by a monoclonal antibody. However, the body can usually replace these cells after the treatment has stopped.

Rituximab (Rituxan)

Rituximab was the first monoclonal antibody approved by the U.S. Food and Drug Administration (FDA) for cancer. Rituximab targets the CD20 antigen, which can be found on the surface of both normal and abnormal cells. The CD20 molecule is a key target for anticancer therapies because it is highly expressed in most B-cell malignancies (i.e., cancers of the white blood cells called B lymphocytes). Rituximab is approved for use in non-Hodgkin lymphoma (NHL) and chronic lymphocytic leukemia (CLL). It is administered by intravenous (IV) infusion and is used either alone or in combination with standard chemotherapy regimens. For example, rituximab is used as *frontline* (initial) therapy with a chemotherapy regimen known as CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) for aggressive B-cell lymphomas such as diffuse large B-cell lymphoma (DLBCL). If initial treatment including rituximab is effective, and either partial or complete remission is achieved, rituximab may then be given alone as an ongoing *maintenance therapy* (treatment used after an initial therapy to maintain the positive effects). Rituximab therapy causes a drop in the number of normal B cells as well as a decrease in the malignant lymphoma cells. Other common side effects of rituximab include infections, fever, and chills.

A subcutaneous form of rituximab (Rituxan Hycela or "rituximab and hyaluronidase human") was approved by the FDA in 2017 for use in patients with previously untreated DLBCL, and those with previously untreated and *relapsed* (disease returns) or *refractory* (disease no longer responds to treatment) follicular lymphoma or CLL.

This new treatment includes the same monoclonal antibody as intravenous rituximab in combination with hyaluronidase human, an enzyme that helps to deliver rituximab under the skin.

Ofatumumab (Arzerra)

Ofatumumab is a monoclonal antibody that also targets the CD20 antigen. Ofatumumab, which is administered by IV infusion, is approved for patients with CLL who have not responded to certain other cancer medications like fludarabine (Fludara) and alemtuzumab (Campath). It is also approved for use as maintenance therapy in patients who had responded at least partially to at least two prior treatments. Finally, ofatumumab is approved in combination with chlorambucil (Leukeran) for the treatment of patients with previously untreated CLL who may not be good candidates for aggressive chemotherapy, and also approved in combination with fludarabine (Fludara) and cyclophosphamide for the treatment of patients with relapsed CLL. The most common side effects of ofatumumab include infusion reactions, infection, low blood cell counts, and upper respiratory tract infection.

Obinutuzumab (Gazyva)

Obinutuzumab is another monoclonal antibody administered by IV infusion that targets CD20 on the surface of B cells. Obinutuzumab is approved in combination with chlorambucil (Leukeran) for the treatment of patients with previously untreated CLL. It is also approved in combination with bendamustine (Treanda) for the treatment of patients with follicular lymphoma (FL) who relapsed or were refractory to a rituximab (Rituxan)-containing regimen. Common side effects of obinutuzumab include infusion reactions, low blood cell counts, coughing, and nausea.

Alemtuzumab (Campath)

Alemtuzumab is a monoclonal antibody that targets the CD52 antigen on the surface of cancerous lymphocytes. Alemtuzumab is approved for the treatment of B-cell CLL and is administered by IV infusion. However, it is provided only through the Campath Distribution Program and is no longer commercially available. Side effects of alemtuzumab include infections (some severe), low blood cell counts, nausea, and insomnia.

Radioimmunotherapy

Radioimmunotherapy (RIT) consists of a targeted antibody attached to a *radioisotope* (a particle that emits radiation). RIT acts as a "guided missile" to destroy lymphoma cells by attaching to them and delivering small doses of radiation.

Ibritumomab Tiuxetan (Zevalin)

Ibritumomab tiuxetan consists of the monoclonal antibody ibritumomab, a radioisotope, and a molecule called tiuxetan that links them together. Like rituximab (Rituxan), ibritumomab tiuxetan targets CD20-expressing B cells. Once the ibritumomab component of the drug has bound to an NHL B cell that expresses CD20, the radioactive component damages the cell, triggering its destruction. Ibritumomab tiuxetan is approved to treat patients with low-grade

or follicular B-cell NHL when the disease relapses or is refractory. It is also used to treat patients with newly diagnosed follicular NHL who have achieved partial or complete responses to *frontline* (initial) chemotherapy. Ibrutinomab tiuxetan is given through an IV infusion in combination with two rituximab treatments. The most common side effects of ibrutinomab tiuxetan include low blood cell counts, fatigue, *nasopharyngitis* (inflammation of the nose), and nausea.

Antibody-Drug Conjugate

An *antibody-drug conjugate* is a monoclonal antibody attached to a chemotherapy drug.

Brentuximab Vedotin (Adcetris)

Brentuximab vedotin targets the CD30 antigen on the cell surface. Brentuximab vedotin enters CD30-positive cells and releases a chemotherapy agent to destroy them. In 2011, brentuximab vedotin became the first new drug approved for the treatment of Hodgkin lymphoma (HL) in almost 35 years. Administered by IV infusion, brentuximab vedotin is approved to treat classical HL (cHL) that has progressed after *autologous stem cell transplantation*, a procedure in which a patient's own immature immune cells are collected before chemotherapy and then reinfused afterwards to replace the healthy blood cells killed by the chemotherapy. Brentuximab vedotin can also be used to treat HL after at least two prior multi-agent chemotherapy regimens in patients who are not candidates for autologous stem cell transplantation. The FDA also approved brentuximab vedotin for *consolidation therapy* (treatment to kill any cancer cells that might remain) after autologous stem cell transplantation of patients with cHL who are considered at high risk of the disease returning or progressing. Brentuximab vedotin is also used for the treatment of systemic anaplastic large cell lymphoma (a type of NHL) after chemotherapy failure. Certain medications (including the antibiotic erythromycin and the anti-epilepsy drug phenytoin) may increase or decrease the function of brentuximab vedotin, so patients on those medications should be monitored carefully. The most common side effects of brentuximab vedotin include low blood cell counts, *peripheral neuropathy* (temporary numbness, tingling, pricking sensations, or sensitivity to touch), anemia, upper respiratory tract infection, fatigue, and nausea.

Cytokines

Cytokines are small signaling molecules released by certain cells of the immune system that coordinate cell-to-cell communication to help regulate the body's immune response.

Interferon Alfa

Interferon alfa (interferon alfa-2a or interferon alfa-2b) is a cytokine that mobilizes the body's immune system to help it fight cancer. Interferon alfa interacts with molecules called receptors on the surfaces of cells to interfere with the cancer cell's ability to divide or to stimulate the immune system to help fight the cancer. It may be given as an injection into a vein or muscle or *subcutaneously* (under the skin). The most common side effects are flu-like symptoms, joint and muscle pain, headache, and nausea and vomiting.

Denileukin Diffitox (Ontak)

Denileukin diffitox is a cytokine drug that directly kills certain lymphoma cells by binding to a protein on the cell surface and then delivering a toxin inside the cell. It is given as an IV infusion. The most common side effects of denileukin diffitox are fever/chills, nausea/vomiting, fatigue, diarrhea, headache, swelling, cough, shortness of breath, and itching. In some cases, patients reported temporary loss of visual acuity or impairment.

Interleukins

Interleukin-11 or oprelvekin (Neumega) is used to stimulate platelet production, which may be decreased by chemotherapy. Platelets are needed to help the blood clot and to prevent bleeding. Oprelvekin is a *supportive therapy*, meaning it helps patients to tolerate chemotherapy, but it has no anticancer activity itself. Oprelvekin is given subcutaneously. Common side effects of oprelvekin include water retention in the hands, feet, and ankles; shortness of breath; increased heart rate; abnormal heart rhythms; and bloodshot eyes.

Interleukin-2 or aldesleukin (Proleukin) is being studied for treating some leukemias and lymphomas. It causes the body to produce more of certain immune cells and prompts these cells to be more effective in fighting the cancer. Aldesleukin is given as an IV infusion. Low blood pressure is a common side effect immediately after the injection of aldesleukin. Other side effects include diarrhea, vomiting, chills, and shortness of breath.

Immunomodulatory Drugs

Immunomodulatory drugs (IMiDs) have many ways of working against tumor cells. They 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.

Lenalidomide (Revlimid)

Lenalidomide is an IMiD that inhibits the growth and induces the death of some types of malignant blood cells, including mantle cell lymphoma (MCL) cells. Lenalidomide should not be taken by pregnant women. Lenalidomide is approved by the FDA for patients with MCL whose disease has returned (relapsed) or progressed (refractory) after two prior treatments (one of which includes bortezomib [Velcade]). Lenalidomide is a capsule which is taken by mouth once daily, with or without food. Some of the most common side effects of lenalidomide include low blood cells or platelets, fatigue, diarrhea, nausea, and coughing.

Checkpoint Inhibitors

The checkpoint inhibitors are a class of immunotherapy that block signaling through proteins present on the surface of some cancer cells that help the cancer avoid detection by the immune system. Two checkpoint inhibitors are currently approved for use in treating lymphoma; however, several others are available to lymphoma patients through clinical trials.

Nivolumab (Opdivo)

Nivolumab is a checkpoint inhibitor that binds to the programmed death receptor-1 (PD-1), thereby allowing the body to launch an immune response against the cancer. It is approved for the treatment of cHL that has relapsed or progressed after autologous stem cell transplantation and post-transplant brentuximab vedotin (Adcetris). Nivolumab is given as an IV infusion. The most common side effects are fatigue, upper respiratory tract infection, fever, diarrhea, and coughing.

Pembrolizumab (Keytruda)

Pembrolizumab also binds to PD-1, thereby allowing the body to launch an immune response against lymphoma cells. It is approved for the treatment of adult and pediatric patients with refractory cHL, or those who have relapsed after three or more lines of therapy. Pembrolizumab is given as an IV infusion. The most common side effects are fatigue, itching, diarrhea, decreased appetite, rash, fever, coughing, shortness of breath, muscle and bone pain, constipation, and nausea.

Please view the Lymphoma Research Foundation's (LRF's) *Immunotherapy and Lymphoma* fact sheet for additional information.

Growth Factors

A growth factor is a signaling protein or hormone that promotes cell growth and differentiation.

Filgrastim (Neupogen)

Filgrastim is a human protein called a granulocyte colony-stimulating factor (G-CSF) that is created inside bacteria. G-CSF does not have anticancer properties, but is given as supportive care to stimulate production of white blood cells either after chemotherapy or before and during stem cell transplantation. Filgrastim is administered by IV infusion or subcutaneously. Side effects include low platelet counts, nausea, and fever.

Epoetin Alfa (Epogen, Procrit)

Epoetin alfa stimulates the growth of red blood cells and is used to treat anemia, which can arise after chemotherapy. Epoetin alfa is administered subcutaneously three times a week during chemotherapy treatment. The most common side effects in patients with cancer on chemotherapy are nausea and vomiting, but other side effects such as muscle, bone, or joint pain and inflammation in the mouth (stomatitis) may also occur.

Biosimilars

When the patent for a prescription medication expires, other companies may create and sell an exact copy of that medication (usually referred to as a *generic drug*) provided at substantially reduced costs. However, replicating biologic drugs is more complicated than making copies of chemically produced medications, because biologic drugs are made in living organisms and are very complex. *Biosimilars* is the term used to describe products that copy biologics. Biosimilars must undergo review by regulatory agencies such as the FDA or the European Medicines Agency (EMA) to demonstrate that they closely resemble the original patented drug molecule and are safe and effective.

Thirty-six biosimilars are available in the European Union as of September 2017 including several products based on G-CSF (filgrastim) for stimulating immune cell growth and several products based on erythropoietin (epoetin) for anemia caused by low red blood cell counts. As of September 2017, seven biosimilars have been approved in the United States: filgrastim-sndz (Zarxio), infliximab-dyyb (Inflectra), adalimumab-atto (Amjevita), etanercept-szss (Erelzi), infliximab-abda (Renflexis), adalimumab-adbm (Cyltezo), and most recently bevacizumab-awwb (Mvasi), the first biosimilar approved for the treatment of cancer. Other biosimilars are under development, such as ones that are similar to the drug rituximab (Rituxan).

Targeted Therapies

Targeted therapies are generally small molecules that affect the biological processes of cancer cells.

Vorinostat (Zolinza)

Vorinostat is an inhibitor of histone deacetylases (HDACs). HDACs are proteins that regulate deoxyribonucleic acid (DNA), influencing which genes are used to make proteins and ultimately affecting the actions of the cell. Some cancer cells make excess HDAC, so inhibiting HDAC can inhibit cancer cell growth or cause cell death. Vorinostat is FDA approved for treating cutaneous T-cell lymphoma (CTCL) in people whose disease has not improved, has gotten worse, or has come back after taking two other therapies. Vorinostat, which is a capsule taken by mouth with food, is currently being tested in other types of lymphoma. The most common side effects are diarrhea, fatigue, nausea, low platelet counts, anorexia, and abnormal taste.

Belinostat (Beleodaq)

Belinostat is also an HDAC inhibitor. It is approved by the FDA to treat patients with relapsed or refractory peripheral T-cell lymphoma (PTCL). Belinostat is given as an IV infusion. The most common side effects are nausea, fatigue, fever, anemia, and vomiting.

Romidepsin (Istodax)

Romidepsin is another HDAC inhibitor. It is FDA approved for treating CTCL and PTCL in patients who have received at least one prior therapy. It acts as a *prodrug*, which means that the drug is *modified* (converted) by the body after it is administered. Romidepsin is given as an IV infusion. Some of the most common side effects include low blood cell or platelet counts, infections, nausea and vomiting, fatigue, and loss of appetite.

Bortezomib (Velcade)

Bortezomib is a targeted agent that inhibits structures inside cells called proteasomes. Inhibition of proteasome activity by bortezomib causes cancer cells to die. Bortezomib is approved by the FDA for treatment of patients with mantle cell lymphoma (MCL). Bortezomib is given as an injection into a vein or under the skin. Certain medications (such as the antibiotic erythromycin or the anti-epilepsy drug phenytoin) may increase or decrease bortezomib function. Common side effects include nausea, diarrhea, low platelet or blood counts, and *neuropathy* (temporary numbness, tingling, pricking sensations, or sensitivity to touch).

Idelalisib (Zydelig)

Idelalisib is a targeted therapy that blocks a protein that relays signals from the outside of a B cell to the inside. The molecule that is inhibited is called phosphoinositide-3-kinase (PI3K)-delta. Normally PI3K-delta transmits signals that help B cells grow, move, divide, and survive. By inhibiting the signal from PI3K-delta, idelalisib helps stop or slow down the growth of lymphoma cells. Idelalisib is FDA approved for the treatment of CLL in combination with rituximab (Rituxan), and for the treatment of follicular B-cell non-Hodgkin lymphoma and small lymphocytic lymphoma (SLL) in patients who were previously treated with at least two other therapies. Idelalisib comes in tablets (pills) that are taken twice a day with or without food. Certain drugs may interfere with idelalisib function and should not be taken at the same time. Patients should check with their physicians or pharmacists about all medications they are taking. It is important that patients adhere to the recommended dosing and treatment regimen for idelalisib. The most commonly reported side effects of idelalisib include diarrhea, pneumonia, fever, feeling tired (fatigue), nausea, cough, abdominal pain, chills, and rash. Serious side effects have occurred when idelalisib is used in combination with some other cancer medicines. Further analysis is still needed, and patients should discuss their options with their physician.

Ibrutinib (Imbruvica)

Ibrutinib targets Bruton tyrosine kinase (BTK), a protein critical for the growth and survival of B cells. Ibrutinib can kill malignant B cell but leave healthy T cells largely unaffected, which distinguishes it from several other treatment methods. Ibrutinib has been approved by the FDA to treat CLL/SLL, CLL/SLL with high-risk DNA mutation called a 17p deletion, marginal zone lymphoma, and Waldenström macroglobulinemia. Ibrutinib is also being studied to treat DLBCL and in patients with lymphoma whose disease has returned (relapsed) or progressed (refractory) after stem cell transplantation. Ibrutinib is taken orally once daily. Common side effects of ibrutinib include diarrhea, muscle and bone pain, rash, nausea, bruising, fatigue, and fever. Some patients taking ibrutinib can develop a serious irregular heart rhythm called atrial fibrillation. Bleeding and bruising risks are also higher with ibrutinib, and the drug can easily

interact negatively with many other medications. It is important for patients and caregivers to review all medications with their physician or pharmacist when using ibrutinib. For optimal results, patients should adhere to the recommended dosing and treatment regimen for ibrutinib.

Venetoclax (Venclexta)

Venetoclax targets Bcl2, a protein that plays a major role in cell survival. Venetoclax has received approval for the treatment of patients with CLL who have the high-risk chromosomal change called 17p deletion and who have received at least one prior line of therapy. The most common side effects are tumor lysis syndrome (metabolic disturbances caused by massive tumor cell death) from rapid shrinkage of disease, low blood cell counts, diarrhea, nausea, and upper respiratory tract infection.

Chimeric Antigen Receptor (CAR) T-Cell Immunotherapy

T cells can be genetically engineered to direct them to attack cancerous B cells with certain biomarkers, such as CD19. In this process, blood cells are collected from the patient, the T cells are isolated, and a chimeric antigen receptor (CAR) protein targeting the biomarker is genetically added to the patient's T cells. Following chemotherapy treatment, the modified T cells are infused back into the patient so they can recognize and kill the malignant cells. The powerful anticancer activity of these special CAR-containing T cells has the potential to create lasting responses. Side effects of CAR T-cell immunotherapy include *cytokine release syndrome* (overactive immune response due to the release of cytokines from cells) and neurotoxicity in the short term. In October 2017, the FDA approved the second gene therapy for cancer, but the first CAR T-cell therapy for patients with certain types of lymphoma. Axicabtagene ciloleucel (Yescarta) is approved to treat adult patients with specific types of B-cell lymphoma who have not responded to (refractory) or who have relapsed after at least two other kinds of treatments.

Ongoing clinical trials, in several subtypes of lymphoma, are actively investigating how to make CAR T-cell immunotherapy better by finding the optimal cell production platform, cell doses, conditioning chemotherapy, and follow-up care.

Novel Therapies Being Tested

Before approval by the FDA or other regulatory agencies, anticancer drug treatments undergo rigorous testing to show that they are effective and safe. After effectiveness and safety are demonstrated in animals, new treatments must be tested in clinical trials of human patients. The drugs and their studies are reviewed by the regulatory agencies before becoming approved treatments. Some patients are able to receive these unapproved therapies by participating in a clinical trial, although which drug the patient receives in the trial is generally randomly assigned, so participation in the trial does not ensure treatment with the new therapy.

Inotuzumab Ozogamicin

Inotuzumab ozogamicin is an immunoconjugate directed against the CD22 antigen on the surface of lymphoma and other cancer cells. Single-agent inotuzumab ozogamicin has demonstrated activity in patients with relapsed B-cell acute lymphoblastic leukemia (ALL) and NHL. In August 2017, the FDA approved inotuzumab ozogamicin for the treatment of relapsed/refractory ALL.

Dinaciclib

A member of a class of novel agents called cyclin-dependent kinase (CDK) inhibitors, dinaciclib has shown activity in high-risk CLL when the disease returns or has stopped responding to treatment. Dinaciclib works by targeting a group of proteins that contribute to cancer cell growth. Dinaciclib may also be active in combination with anti-CD20 monoclonal antibodies like rituximab (Rituxan) and ofatumumab (Arzerra).

Other Possible Emerging Treatments

Treatment options are changing as new therapeutics are becoming available and current treatments are improved. Some of the monoclonal antibodies that target various other antigens found on lymphoma cells are being investigated for the management of lymphoma, and the use of vaccines to stimulate the body's immune system to respond to the invasion of cancer cells – not prevention – are being investigated. Many of the biologic agents described in this fact sheet are also under investigation for the treatment of other types of lymphoma. Because today's scientific research is continuously evolving, 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.

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 and CLL/SLL, 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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