LYMPHOMA
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Getting the Facts

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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 targeted than conventional chemotherapy, which generally kills any rapidly dividing cell in the body. The term "biologics" refers to complex molecules produced in living cells (e.g., bacteria, yeast cells, or purified mammalian cells maintained in the laboratory). Biologic agents are often used in combination with chemotherapy regimens. Specific agents are used to target particular characteristics of cancer cells. If a patient's tumor does not have the necessary target (e.g., a specific protein on the surface of the cancer cell), the drug may not be effective.

Immunotherapy

Monoclonal Antibodies

Monoclonal antibodies are the most common biologic agents used for lymphoma therapy. 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 destroy the tumor cell. Conjugated antibodies bring a drug, *radioactive* (giving off radiation) particle, or toxic chemical to its target on the malignant cell by recognizing the antigen on the tumor cell and transporting the agent to the cell.

Some of the monoclonal antibodies' targets are on normal cells as well as the malignant cells. If a target is on normal cells, the normal cells can also be harmed by a monoclonal antibody, but 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 is 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). Rituximab is administered by intravenous (IV) infusion and is used either alone or in combination with standard chemotherapy regimens. For example, rituximab is used as *first-line* (initial) therapy with CHOP (cyclophosphamide, doxorubicin, vincristine, and 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 as an ongoing maintenance therapy. With rituximab therapy, there is a drop in the number of normal B cells as well as a decrease in the malignant lymphoma cells. Other common side effects with rituximab include infections, fever, and chills.

Ibritumomab Tiuxetan (Zevalin)

Radioimmunotherapy (RIT) consists of a targeted antibody with a source of radiation attached. RIT acts as a "guided missile" to destroy lymphoma cells by attaching to them and delivering small doses of radioactivity. Ibritumomab tiuxetan consists of the monoclonal antibody ibritumomab linked via an intermediary molecule to a radioactive particle. Like rituximab, ibritumomab tiuxetan targets CD20-expressing B cells. The ibritumomab component of the drug specifically binds to NHL B cells that express CD20. Once bound, 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* (returns after prior treatment) or is *refractory* (no longer responds to treatment), and to treat patients with newly diagnosed follicular NHL who have achieved partial or complete responses to first-line chemotherapy. Ibritumomab tiuxetan is given through an IV infusion in combination with two rituximab treatments. Response to therapy (as measured by reductions in tumor size) was higher in patients receiving ibritumomab tiuxetan plus rituximab than rituximab alone. The most common side effects with ibritumomab tiuxetan include low blood cell counts, fatigue, and nausea.

Ofatumumab (Arzerra)

Ofatumumab is a monoclonal antibody that also targets the CD20 antigen on the cell surface. Ofatumumab, administered by IV infusion, is approved for patients with CLL who have not responded to certain other cancer medications (e.g., fludarabine and alemtuzumab). As maintenance therapy in patients who had responded at least partially to at least two prior treatments, ofatumumab treatment was compared to *observation* (watching a patient's condition but not giving treatment unless symptoms appear or change) and resulted in survival without *disease progression* (worsening) that was almost twice as long (29 months compared with 15 months) as in those not receiving therapy. It is therefore approved for treatment in this situation and is also approved in combination with chlorambucil (Leukeran) for the treatment of previously untreated CLL patients who may not be good candidates for aggressive chemotherapy. The most common side effects with ofatumumab include infection, low blood cell counts, and fever.

Obinutuzumab (Gazyva)

Obinutuzumab is another monoclonal antibody administered by IV infusion and designed to target CD20 on the surface of B cells. Obinutuzumab is approved for treatment of previously untreated CLL, in combination with the drug chlorambucil. It is also approved in combination with bendamustine (Treanda) for the treatment of patients with follicular lymphoma (FL) who relapsed or are refractory to a rituximab-containing regimen. Obinutuzumab is administered by IV infusion. In a clinical trial of patients with CLL and other medical conditions, the combination treatment was compared to treatment with chlorambucil alone. Chlorambucil-combination treatment with obinutuzumab was somewhat more effective than chlorambucil-combination treatment with rituximab in a clinical trial of patients with the characteristics described above. In a clinical trial of patients with FL, patients receiving bendamustine alone or obinutuzumab in combination with bendamustine had comparable overall response rates (75% vs 79%, respectively). Common side effects with obinutuzumab include low blood cell counts, fever, and nausea.

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Alemtuzumab (Campath)

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

Brentuximab Vedotin (Adcetris)

Brentuximab vedotin, an *immunoconjugate* (monoclonal antibody with a chemotherapy drug attached), 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. Brentuximab vedotin, administered by IV infusion, is used to treat HL that has progressed after *autologous stem cell transplantation* (a procedure in which a patient's own immature immune cells are collected before chemotherapy and later transplanted back in the hope that they mature and are able to replace the function of the cells lost to cancer and/or chemotherapy), or after at least two prior multi-agent chemotherapy regimens in patients who are not candidates for stem cell transplantation. The FDA approved brentuximab vedotin for *consolidation treatment* (treatment to kill any cancer cells that might remain) after post-autologous stem cell transplantation of patients with HL who are considered at high risk of the disease coming back or progressing. Brentuximab vedotin is also used for the treatment of systemic anaplastic large cell lymphoma (a type of NHL) after chemotherapy failure. The drug is administered by IV infusion. Certain drugs (including the antibiotic erythromycin and the anti-epilepsy drug phenytoin) may increase or decrease the function of the chemotherapeutic agent in brentuximab vedotin, so patients on these other drugs should be watched carefully. The most common side effects with brentuximab vedotin include low blood cell counts, nerve damage leading to neuropathy, anemia, fatigue, and nausea.

Cytokines

Interferon Alfa

Interferon alfa (interferon alfa-2a or interferon alfa-2b) is a signaling molecule, called 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. Interferon alfa may interfere with the cancer cell's ability to divide or may 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, fatigue, low blood cell counts, low calcium, high glucose, high triglycerides, changes in liver enzyme levels, weight loss, and hair loss.

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 prevent bleeding. Oprelvekin is a *supportive therapy*, meaning it helps patients to tolerate chemotherapy, but has no anticancer activity itself. Oprelvekin is given as an injection under the skin. 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 use against 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 common side effects include diarrhea, vomiting, chills, and shortness of breath.

Denileukin Diftitox (Ontak)

Denileukin diftitox is a cytokine drug that directly kills certain lymphoma cells by binding to a protein on the cell surface and then delivering a poison inside the cell. It is given as an IV infusion. The most common side effects of denileukin diftitox are fever/chills, nausea/vomiting, fatigue, diarrhea, headache, swelling, cough, shortness of breath, and itching.

Immunomodulatory Drugs

Lenalidomide (Revlimid)

Lenalidomide is an immunomodulatory drug (IMiD) that seems to have many ways of working against tumor cells. It causes tumor cells to die, helps keep the tumor from getting nutrients from the blood, and stimulates the immune system. Lenalidomide is related to the drug thalidomide and should not be taken by pregnant women. Lenalidomide is approved by the FDA for patients with mantle cell lymphoma (MCL) that comes back or gets worse after two prior treatments (one of which includes bortezomib). It is taken by mouth once daily, with or without food. Some of the most common adverse events with this drug include fatigue, diarrhea, nausea, and cough.

Checkpoint Inhibitors

The checkpoint inhibitors are a new class of immunotherapy that block signaling through checkpoints, which are used by some cancers to evade detection by the immune system. Several checkpoint inhibitors are currently available for lymphoma patients through clinical trials. Please view the Lymphoma Research Foundation's (LRF's) *Immunotherapy and Lymphoma* fact sheet for additional information.

Nivolumab (Opdivo)

Nivolumab is a checkpoint inhibitor that binds to the PD-1 receptor thereby allowing the body to launch an antitumor immune response. It is approved for the treatment of HL that has relapsed after autologous stem cell transplantation and post-transplantation brentuximab vedotin. Nivolumab is given as an IV infusion. The most common side effects are fatigue, upper respiratory tract infection, fever, diarrhea, and cough.

Growth Factors

Filgrastim (Neupogen)

Filgrastim is a human protein called granulocyte colony-stimulating factor (G-CSF), produced in bacteria. G-CSF is given as supportive care to stimulate production of white blood cells after chemotherapy has reduced the levels of these cells or before and during autologous stem cell transplantation. Filgrastim is administered by IV infusion or as an injection under the skin. 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. Anemia can also arise after chemotherapy. Epoetin alfa is administered by injection under the skin three times a week, during chemotherapy treatment. Epoetin alfa is well-tolerated. Most side effects were not much more common than occurred with placebo treatment in the same clinical trials.

Biosimilars

Upon expiration of a patent for an original prescription drug, other companies are welcome to create and market a copy of the drug

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(usually referred to as a *generic drug*). Generic drugs are generally provided at substantially reduced costs. Replicating the manufacture of biologic drugs is more complicated than that of chemically produced drugs, because of the biologic drugs' production in living organisms and the complexity of the products themselves. *Biosimilars* is the term used to describe products that copy biologics. Generics and biosimilars must undergo review by regulatory agencies like the FDA in the United States and the European Medicines Agency (EMA) in the European Union to demonstrate that they closely resemble the original patented drug molecule and are safe and effective.

Biosimilars available in the European Union include several products based on G-CSF (filgrastim) for stimulating immune cell growth, and several products based on erythropoietin (epoetin) for anemia caused by too few red blood cells. As of April 2016, only two biosimilars had been approved in the United States: filgrastim-sndz (Zarxio) and infliximab-dyyb (Inflectra). Approval by the FDA (facilitated by the Biologics Price Competition and Innovation Act) was based on scientific and clinical data, demonstrating that Zarxio is highly similar to, with no clinically meaningful differences from, the US-licensed reference product filgrastim (Neupogen). Other biosimilars are under development, such as ones that are similar to the drug rituximab.

Targeted Therapies

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

Vorinostat (Zolinza)

Vorinostat is an inhibitor of histone deacetylases (HDAC). HDACs are proteins that regulate deoxyribonucleic acid (DNA), influence which genes are used to make proteins, and ultimately influence the actions of the cell. Some cancer cells make excess HDAC, and its inhibition is seen to inhibit tumor-cell growth or to cause tumor-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 other medications. Vorinostat is currently being tested in other types of lymphoma. Vorinostat is given as a tablet that is taken by mouth with food. It is also given in combination with other drugs to treat patients with lymphoma. The most common side effects are fatigue, diarrhea, nausea, and abnormal taste.

Belinostat (Beleodaq)

Belinostat is also an HDAC inhibitor. Belinostat is approved by the FDA to treat patients with relapsed or refractory peripheral T-cell lymphoma (PTCL). It is given as an IV infusion for five days every three weeks. 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 had received at least one prior therapy. It acts as a *prodrug*, which means that the drug is modified by the body after it is administered. Romidepsin is given as an IV infusion. The most common adverse events with this drug are low blood cell 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 tumor cells to die. Bortezomib is approved by the FDA for treatment of patients with MCL. Bortezomib is given as an injection into a vein or under the skin. Certain drugs (such as the antibiotic erythromycin or the anti-epilepsy drug phenytoin) may increase or decrease bortezomib function, so patients on these other drugs must be watched carefully. Other common side effects include nausea, diarrhea, fatigue, and *peripheral 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 membrane of a B cell to the inside workings of the cell. 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 and for the treatment of follicular B-cell NHL (FL) and small lymphocytic lymphoma (SLL), both in patients who were previously treated with other medications. Idelalisib comes in tablets that are swallowed 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.

Its most commonly reported side effects include diarrhea, fever, fatigue, nausea, cough, pneumonia, abdominal pain, chills, and rash. As of April 2016, certain clinical trials, in the *front-line* (initial) setting using idelalisib in combination with another therapy, for patients with indolent NHL and CLL/SLL were stopped to further evaluate increased adverse events that appeared to be the result of combining idelalisib with other cancer medicines. Further analysis is still needed, and patients should discuss options with their physician.

Ibrutinib (Imbruvica)

Ibrutinib targets Bruton tyrosine kinase (BTK), a protein critical for the growth and survival of B cells. This allows ibrutinib to kill malignant B cells but leave healthy T cells largely unaffected, which distinguishes it from several other treatment methods. Ibrutinib has been approved by the FDA to treat MCL, CLL/SLL, CLL with a specific DNA mutation (a deletion of DNA on chromosome 17), and a type of NHL called Waldenström macroglobulinemia (WM). It is being studied in DLBCL. Ibrutinib is taken orally once daily. Common side effects with ibrutinib include diarrhea, upper respiratory tract infection, fatigue, and fever. Some patients can develop a serious irregular heart rhythm called atrial fibrillation also referred to as AFib. Bleeding and bruising risks are also higher with ibrutinib which can easily interact adversely with a lot of other medications. It is important for patients and caregivers to review all medications with their physician and/or pharmacist when ibrutinib is being taken.

Venetoclax (Venclexta)

Venetoclax targets *Bcl2*, a protein that plays a major role in cell survival. It has received approval for the treatment of patients with CLL who have a high-risk chromosomal change in their CLL cells called 17p deletion, and who have received at least one prior line of therapy. The most common adverse reactions are tumor lysis syndrome from rapid shrinkage of disease, mild diarrhea, upper respiratory tract infections, nausea, and low blood cell counts.

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

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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 October 2015, the FDA granted Breakthrough Therapy designation (that comes with expedited review) for inotuzumab ozogamicin in ALL, based on the results of a trial that enrolled 326 adult patients with relapsed or refractory CD22-positive ALL and compared inotuzumab ozogamicin to standard of care chemotherapy.

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 has also shown promise when combined with the anti-CD20 monoclonal antibodies rituximab or ofatumumab (discussed earlier).

Chimeric Antigen Receptor (CAR) T-Cell Immunotherapy

The cancer cell killing potential of T cells can be genetically engineered to direct T cells to attack cancerous B cells with certain biomarkers, such as CD19. Through this process, blood cells are collected from the patient, T cells are isolated, and a chimeric antigen receptor (CAR) protein targeting the biomarker is genetically introduced into the patient's T cells. After the T cells are infused back into the patient (following chemotherapy treatment) they can recognize and kill the malignant cells. The powerful antitumor responses of these special CAR-containing T cells could be durable because these modified T cells can potentially survive for a long time.

Other Possible Emerging Treatments

Other monoclonal antibodies that target various other antigens found on lymphoma cells are being investigated for the management of lymphoma. All of the biologic agents described here are also under investigation for the treatment of other types of lymphoma. Vaccine therapy is under investigation for the treatment—not prevention—of lymphoma. The vaccines are used to stimulate the body's immune system to respond to the invasion of cancer cells.

Treatment options are changing as new therapeutics are becoming available and current treatments are improved. 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, 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.

Follow-up

Patients in remission 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, positron emission tomography [PET] scans, and computed tomography [CT] scans) may be required at various times during remission to evaluate the need for additional treatment.

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 effects resulting from treatment or potential disease recurrences.

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, including our award-winning mobile app. LRF also provides many educational activities, from in-person meetings to teleconferences and webcasts, as well as disease-specific websites, videos, and e-Updates for current lymphoma and CLL information 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.