

Immunotherapy Facts

No. 9 in a series providing the latest information for patients, caregivers and healthcare professionals

Highlights

- In recent years, progress in understanding the natural immune system has led to research and development for a type of treatment for blood cancer called “immunotherapy.”
- Immunotherapy is based on the concept that immune cells or antibodies that can recognize and kill cancer cells can be produced in the laboratory and then given to patients to treat cancer. Several types of immunotherapy are either approved for use or are under study in clinical trials to determine their effectiveness in treating various types of cancer.
- When immunotherapy is used in cancer treatment, it is usually given in combination with chemotherapy or other cancer treatments. It may be used as maintenance therapy following combination chemotherapy, and in some circumstances it is used as a single agent to treat cancer.
- Immunotherapy generally results in fewer short-term side effects than chemotherapy. However, certain side effects are associated with the various types of immunotherapy.
- Monoclonal antibodies, a type of immunotherapy, are made in the laboratory. Monoclonal antibodies may be used alone, or they may have an attached drug or radioactive material.
- Cancer vaccines, another type of immunotherapy, stimulate the body’s immune system to destroy cancer cells.
- Natural chemicals made by the body called “cytokines” stimulate or inhibit certain cell activities. Cytokines called “interferons” and “interleukins,” which increase the production of immune cells, can be made in the laboratory and given to patients as part of treatment for cancer.
- Donor lymphocyte infusion is another type of immunotherapy. Lymphocytes from the blood of a donor are collected and then infused into a patient who has already had an allogeneic stem cell transplant from that same donor.
- Reduced-intensity allogeneic stem cell transplantation is another immunotherapy approach. While a standard allogeneic transplant uses the pretransplant treatment to destroy most of the patient’s disease cells, a reduced-intensity transplant relies on the donor immune cells to fight disease.
- While great strides have been made in understanding the role of the immune system in cancer, the science is still new compared to advances in other cancer treatments. Research in clinical trials is ongoing to develop ways to use immunotherapy in cancer therapy.

Introduction

This fact sheet gives an overview of several types of immunotherapy and their role in the treatment of blood cancer. A brief introduction to the natural immune system is included to help readers understand the immunotherapy information that follows.

The natural immune system

The body's natural immune system includes a network of cells and organs that help to defend the body from "antigens." Antigens are substances that are foreign to the body; they stimulate the production of proteins called "antibodies," which target specific antigens. Invading bacteria, viruses, fungi and allergens are examples of antigens. The production of antibodies to attack specific antigens is part of the body's natural immune response. Autoimmune diseases, such as lupus and rheumatoid arthritis, arise from an overactive immune response to substances in the body.

An antigen stimulates an immune response (antibody production) when it is ingested or inhaled or comes into contact with the skin or mucous membranes. The antibodies coat, mark for destruction, or inactivate bacteria, viruses, harmful toxins or other foreign particles. Monoclonal antibody therapies, described on page 3, are laboratory-produced proteins designed to mimic the natural antibodies produced during an immune response.

The immune cells that play a role in the body's immune response include

- B lymphocytes (also called "B cells"), which make the antibodies that recognize and target antigens. B lymphocytes are found in the marrow and other parts of the lymphatic system.
- T lymphocytes (also called "T cells"), which have several functions, including helping B lymphocytes to make antibodies against invading microbes.
- Natural killer cells (also called "NK cells"), which attack cells infected by microorganisms and kill cancer cells. NK cells are called "natural killers" because they do not need to recognize a specific antigen in order to attack and destroy.
- Phagocytes, which swallow and digest microscopic foreign particles, bacteria and dead or dying cells. Neutrophils, macrophages and dendritic cells are all types of phagocytes.

Cancer and the immune system

In most circumstances, the body's natural immune system does not seem to identify cancer as foreign to the body. One reason for this is that cancer cells are not external invaders, as are viruses and bacteria. Instead, cancer cells are altered versions (mutations) of normal cells. As such, a cancer cell may not present a unique feature (for example, an antigen) to trigger an immune response.

Cancer cells appear to be composed almost entirely of the same structures as normal cells. One of the challenges for researchers in developing new and better cancer therapies is to learn more about the differences between cancer cells and normal cells. Any difference in structure that can be identified as unique to the cancer cell will help researchers to develop treatments that destroy cancer cells but are not toxic to normal cells.

Another issue is that cancer cells may suppress immune activity. This factor may contribute to the immune system's failure to recognize cancer cells as foreign. Certain cancers, such as lymphoma, may occur in patients whose immune system is depressed by disease or drug therapies.

Immunotherapy, also called “biological therapy,” is a promising treatment and an active area of cancer research for people with certain types of blood cancer. The development of immunotherapies is based on the concept that immune cells or their products (such as antibodies) that can recognize and kill cancer cells can be made in the laboratory and given to patients to treat cancer. Several types of immunotherapy are either approved treatments or are under study in clinical trials to determine their effectiveness in treating various types of blood cancer.

Immunotherapies generally cause less severe short-term side effects than most chemotherapy or radiation therapy, which not only destroys cancer cells but also affects rapidly dividing normal cells. It is the effect of chemotherapy on normal cells that results in hair loss, mouth sores, nausea, reduced resistance to infection and other side effects.

Types of Immunotherapy

Immunotherapies for blood cancer that are in use or under study include

- Monoclonal antibody therapy, including radioimmunotherapy, a type of monoclonal antibody therapy that combines radiation therapy with a monoclonal antibody
- Interferons and interleukins
- Donor lymphocyte infusion
- Reduced-intensity allogeneic stem cell transplantation
- Therapeutic cancer vaccines.

When immunotherapy is used to treat cancer, it

- Is most often given in combination with other types of cancer treatment
- May be used as maintenance therapy following combination chemotherapy
- Is used as a single agent in some cases to treat individuals with blood cancer.

Monoclonal antibody therapy

Monoclonal antibodies are laboratory-made immunoglobulins (proteins that help the body fight infection) that are used to

- Target and attack cancer cells
- Deliver toxins (anticancer drugs or radiation) directly to cancer cells with less harm to healthy cells.

Monoclonal antibody therapy is sometimes referred to as “passive immunotherapy,” which means that it does not directly stimulate a patient’s immune system to respond to a disease. Instead, a monoclonal antibody therapy mimics the natural antibodies made by the body. The drug attacks a specific target or marker on the surface of a cancer cell. A monoclonal antibody is also called a “targeted therapy” because it is directed to a single target on the cancer cell.

The monoclonal antibody binds to the target on the cell and, in so doing, blocks or interferes with the activity of the cancer cell. The target for the antibody on the cell surface is referred to by the letters *CD* (“cluster designation”) and a number. For example, the monoclonal antibody rituximab (Rituxan®) targets CD20 on B lymphocytes. The monoclonal antibody alemtuzumab (Campath®) targets CD52 found on T and B lymphocytes, NK cells and monocytes.

All new drugs must show proof that they are safe and effective before they can be approved by the US Food and Drug Administration (FDA). Rituxan, initially FDA approved in 1997, is indicated for non-Hodgkin lymphoma. It is also used to treat patients who have chronic lymphocytic leukemia, Waldenström macroglobulinemia and autoimmune diseases. Campath was first approved by the FDA in 2001 for the treatment of B-cell chronic lymphocytic leukemia.

Monoclonal antibody therapies are usually given to individuals in an outpatient setting. The drug is infused through a needle placed in a vein (“intravenous infusion,” or “IV”) in the patient’s arm. The doctor may prescribe medicines before each infusion to reduce certain side effects. The doctor will also do regular blood tests to check for other side effects.

Side effects such as fever and chills, tiredness, headache and nausea are among the most commonly reported reactions to Rituxan and Campath. Other less common, but more severe, side effects include shortness of breath, a drop in blood pressure, an irregular heartbeat, chest pain and low blood cell counts.

Monoclonal antibody therapies are sometimes referred to as “naked” or “conjugated.” A naked monoclonal antibody therapy does not have another chemical or radioactive material attached to it. Rituxan and Campath are examples of naked monoclonal antibody therapies.

More information about Rituxan is available at www.gene.com/gene/products/information/pdf/rituxan_med_guide.pdf.

More information about Campath is available at www.campath.com/ConsideringCampath/AdminAndDosing.html.

A conjugated monoclonal antibody therapy consists of a monoclonal antibody with a radioactive substance, a toxin or another therapeutic agent. One example of a conjugated monoclonal antibody is gemtuzumab ozogamicin (Mylotarg®), which was FDA approved in 2000 to treat adults aged 60 years or older with CD33-positive acute myelogenous leukemia (AML) in first relapse. Mylotarg combines a powerful chemical toxin called “calicheamicin” with a monoclonal antibody that targets the antigen CD33 on myeloid blast cells.

The monoclonal antibody delivers the calicheamicin to the leukemic cells with the CD33 antigen; then the calicheamicin acts as a chemotherapeutic agent. Calicheamicin is classified as an “antitumor antibiotic.” Other drugs in the same class that are used to treat people with AML include daunorubicin (Cerubidine®), doxorubicin (Adriamycin®), idarubicin (Idamycin®) and mitoxantrone (Novantrone®).

The side effects of Mylotarg include a decrease in blood cell production in the marrow that results in low red cell counts and low blood platelets, swelling of the membrane inside the mouth, liver problems and rash.

More information about Mylotarg is available at www.mylotarg.com/products.

Radioimmunotherapy

Radioimmunotherapy is another type of conjugated monoclonal antibody therapy.

An anti-CD20 monoclonal antibody can be linked to a radioactive isotope (either radioactive yttrium or radioactive iodine) to deliver radiation directly to cancer cells. Ibritumomab (Zevalin®), FDA approved in 2002, and tositumomab and iodine I 131 tositumomab (Bexxar®), FDA approved in 2003, are examples of this treatment, which is also called “radiolabeled monoclonal antibody.”

Zevalin is indicated for adults with previously untreated follicular NHL who achieve a partial or complete response to first-line chemotherapy, and for adults with relapsed or refractory, low-grade or follicular B-cell non-Hodgkin lymphoma (NHL), including those with Rituxan-refractory follicular NHL. Its safety and effectiveness in children have not been established.

Bexxar is indicated for adults with CD20 antigen-expressing relapsed or refractory, low-grade, follicular or transformed NHL, including adults with Rituxan-refractory NHL; its safety and effectiveness in children have not been established.

Zevalin and Bexxar are being studied in clinical trials

- For use with chemotherapy as possible therapies for newly diagnosed patients with follicular lymphoma
- As therapy for aggressive forms of NHL in combination with or following other drug regimens
- As part of high-dose therapy programs along with autologous stem cell support.

In most cases, patients are treated with Zevalin or Bexxar in an outpatient facility. The course of treatment can usually be completed in a one- to three-week period. Each treatment can take several hours to complete. Radioimmunotherapy does not cause hair loss, often does not cause nausea and causes only mild degrees of fatigue and lowered blood counts. The recovery period is generally quite brief.

Before receiving the treating dose of radioimmunotherapy, the patient will receive preparatory infusions of non-radiation-linked antibody and then low-dose radiation-linked antibody. A few scans are usually obtained over the next several days to show the radiolabel at sites of disease. Then, on treatment day, the patient again receives the antibody by IV, but this time a full dose of the radiation is attached.

Occasionally, patients may have a severe allergic reaction to the infusion. This and other risks should be discussed with the doctor. Fever, chills and aches can occur after the treatment is received. Patients may be given drugs to reduce these effects.

Patients will need to have routine blood work for a few months after receiving the treatment to ensure full blood count recovery. For most patients, the production of blood cells is decreased for a period of time. This is usually a mild to moderate reduction that does not last. Patients who have had chemotherapy and/or external radiotherapy before receiving radioimmunotherapy may experience a greater degree of cytopenia (low blood counts) after radioimmunotherapy.

Other reactions may include low blood pressure, diarrhea or rash. Rash or swelling at the site of the injection affects some patients. These reactions also tend to be mild to moderate and are short-lived. Some patients treated with Zevalin or Bexxar may experience nausea and vomiting. However, anti-nausea drugs are given that help to prevent this reaction. Patients are also given iodide prior to receiving radioactive iodine-linked antibodies. The iodide is taken by mouth (orally) and is well tolerated. The purpose of giving the iodide is to prevent the radioactive iodine from being taken up by the thyroid gland. The thyroid gland normally takes up iodide because it is used to make thyroid hormone.

Patients being treated with radioimmunotherapy need to take certain easily understood precautions to protect the people around them from exposure to radiation. The precautions are not very restrictive; the specific instructions and the length of time the precautions are needed depend on whether the patient is treated with Zevalin or Bexxar. The doctor and nurse will explain the precautions. It is important for patients to ask members of their oncology team any questions they may have.

Radioimmunotherapy works gradually, and it may take several months for cancer cells to die and tumors to shrink. The effects of treatment are monitored with physical examinations and imaging tests, such as CT scans and PET scans.

Overall, radioimmunotherapy is usually well tolerated.

More information about Zevalin is available at www.zevalin.com.

More information about Bexxar is available at www.bexxar.com.

Interferons and interleukins

Interferons and interleukins are natural chemicals called “cytokines.” These chemicals are secreted by various types of cells and act on other cells to stimulate or inhibit certain actions of the cells. Cytokines that increase production of immune cells can be made in the laboratory and given to patients as part of treatment for infection and cancer. Interferons and interleukins are sometimes referred to as “nonspecific immunotherapies.”

Interferons (such as interferon-alpha) are proteins produced by lymphocytes that help the body resist infections and cancers. Interferon-alpha is the most widely used interferon in cancer treatment. High-dose interferon-alpha acts like a chemotherapeutic agent in blocking cancer cell growth. Interferon-alpha may be used to treat some people who have hairy cell leukemia, chronic myelogenous leukemia, non-Hodgkin lymphoma or cutaneous T-cell lymphoma.

Interferon-alpha is generally administered every day or several days a week. It is injected subcutaneously (under the skin). Newer formulations of interferon (called “pegylated interferon”) are now available with once-a-week dosing. Since interferons stimulate the body’s own defenses, researchers are exploring combinations of interferon-alpha and other immune modifiers or chemotherapy.

Interleukins are proteins produced by lymphocytes that activate the growth and activity of many immune cells, such as lymphocytes, that can destroy cancer cells. One of the interleukins, IL-2, is being studied for use in treating patients with leukemia, lymphoma or myeloma.

Side effects of therapy with interferons or interleukins may include high fever, chills, aches and fatigue. IL-2, particularly in high doses, can cause fluid to accumulate in the body so that the person swells up and can feel quite sick. Some patients may need to be hospitalized because of this problem.

Donor lymphocyte infusion

Donor lymphocyte infusion is another type of immunotherapy. Lymphocytes from the blood of a donor are collected and then infused into a patient who has already had an allogeneic stem cell transplant from that same donor. The donor and the recipient are very similar (but not identical) in tissue type. As a result, the donor lymphocytes may identify the recipient’s cells as targets for attack.

Donor lymphocyte infusion is usually done on an outpatient basis. It has mainly been used to treat relapsed chronic myelogenous leukemia, although patients with relapsed acute leukemia, chronic lymphocytic leukemia, Hodgkin lymphoma, non-Hodgkin lymphoma or myeloma may also receive this treatment.

A potential risk of donor lymphocyte infusion is severe graft-versus-host disease (GVHD), in which the recipient's tissues (such as the skin, liver or gastrointestinal tract) are attacked by the donated immune cells.

Reduced-intensity allogeneic stem cell transplantation

Reduced-intensity allogeneic stem cell transplantation is another immunotherapy approach. Patients being prepared for a reduced-intensity allogeneic stem cell transplant (also called a "nonmyeloablative transplant") receive less intense conditioning treatment than with a standard allogeneic transplant. While a standard transplant uses the pretransplant treatment to destroy most of the patient's disease cells, a reduced-intensity transplant relies on the donor immune cells to fight disease. The effectiveness of reduced-intensity transplants depends on the graft-versus-tumor (GVT) effect, in which the recipient's new immune system (originating from the donated stem cells) may destroy the bulk of remaining cancer cells. This reduced-intensity dosing is also more tolerable to older patients who would otherwise not do well with high-dose chemotherapy.

The procedure uses low rather than very high doses of either radiation or chemotherapy to condition the patient. Potent immune therapy is given to suppress the recipient's T lymphocytes to avoid rejection of the donor stem cells. The goal is to have the donor stem cells take up residence in the recipient's marrow and produce lymphocytes (immune cells) that attack the patient's blood cancer cells. If successful, the immune cells made from the donor's stem cells attack and suppress the recipient's remaining cancer cells.

In addition to older patients, reduced-intensity transplantation may be advantageous for

- Patients with less rapidly progressive blood cancers
- Patients with certain infections where prolonged marrow suppression would be detrimental
- Patients with additional serious medical conditions.

Because reduced-intensity transplantation is relatively new, its risks and benefits have not yet been clearly established. As is the case with allogeneic stem cell transplantation, GVHD is a potential concern. Patients interested in exploring the possibilities of a nonmyeloablative transplant should speak to their doctors about whether participating in a clinical trial would be an appropriate step for them.

Therapeutic cancer vaccines

A vaccine that prevents a disease, such as measles, mumps or tetanus, contains the same antigen (or part of the antigen) that causes the disease, but the vaccine antigen is either killed or very weak. The vaccine antigen is not strong enough to produce the symptoms and signs of the disease, but it is strong enough so that the body reacts by making antibodies. The antibodies prevent infection if a person is exposed to the antigen in the future.

Unlike conventional vaccines that are used to prevent infectious diseases, cancer vaccines are designed to treat cancer. Vaccines for leukemia, lymphoma and myeloma are still in development and are only available through clinical trials. Most cancer vaccine studies involve giving a patient chemotherapy or other standard cancer therapy to reduce the amount of disease in the body before administering the vaccine.

Ideally, therapeutic cancer vaccines will destroy any remaining cells after other types of cancer treatment and help prevent the disease from returning. Some therapeutic cancer vaccines are also being studied in patients who are being monitored with “watchful waiting.” The objective of such studies is to see if early vaccine treatment is more beneficial than waiting until the disease shows evidence of progression before beginning treatment.

For detailed information about how cancer vaccines work, see the free LLS fact sheet *Vaccine Therapy*.

Questions to Ask Your Doctor About Immunotherapy

People living with blood cancers can use the following questions as a guide to discuss immunotherapy with members of their oncology team:

- Why are you recommending this type of therapy?
- Are there any risks with this therapy?
- How does this treatment work to treat my disease?
- How will this treatment be given to me?
- How often will I get this treatment?
- What is the period of time that I need to be on this treatment?
- How will you know if this therapy is working?
- What side effects should I expect during and/or following my therapy?
- Will the treatment cause pain?
- Will I need to make changes to my daily routine, work or exercise?
- Will my health plan cover this therapy?
- Will I need other cancer treatment? If so, will I receive these therapies together or at different times?
- Are there any clinical trials involving this therapy that are suitable for me?

A printable list of questions about treatment is available at www.LLS.org/whattoask. Click on “Healthcare Question Guides” and then click on the “treatment options” guide.

Clinical Trials

Clinical trials are conducted under rigorous guidelines to help doctors determine the benefits of new treatments and what, if any, side effects can be expected. In these trials, new drugs, new types of targeted therapies and new approaches to stem cell transplantation are being explored in order to bring better treatments to people with various types of blood cancers and thus improve their quality of life. New approaches to treatment, many of which are being supported by LLS research programs, hold the promise of increasing the rate of remission and finding a cure for many blood cancers.

The Information Resource Center at LLS offers guidance on how patients can work with their doctors to find out if a specific clinical trial is an appropriate treatment option. For information about specific drugs in clinical trials, contact the Information Resource Center at LLS via the Web site, www.LLS.org; email, infocenter@LLS.org; or phone, (800) 955-4572.

We're Here to Help

LLS is the world's largest voluntary health organization dedicated to funding blood cancer research, education and patient services. LLS has chapters throughout the country and in Canada. To find the chapter nearest you, visit our Web site, www.LLS.org, or contact

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Callers to the Information Resource Center may speak directly with an Information Specialist, Monday to Friday, 9 a.m. to 6 p.m., ET. They may also contact an Information Specialist by clicking on "Live Help" (10 a.m. to 5 p.m., ET) at www.LLS.org or by sending an email to infocenter@LLS.org. Information Specialists can answer general questions about diagnosis and treatment options, offer guidance and support and assist with clinical trial searches for leukemia, lymphoma, myeloma, myelodysplastic syndromes and myeloproliferative diseases. The LLS Web site has information about how to find a clinical trial, including a link to TrialCheck®, a clinical trials search service provided by LLS.

LLS also provides fact sheets and booklets that can be ordered at (800) 955-4572 or through www.LLS.org/freematerials.

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