

Immunotherapy

No. 9 in a series providing the latest information on blood cancers

In recent years, progress in understanding and regulating the natural immune system has led to the research and development of new treatments for blood cancers called immunotherapies. For example, researchers have learned that the beneficial effects of stem cell transplantation, for patients with chronic myelogenous leukemia, myeloma and other blood cancers, is related to the attack of donor immune cells on the recipient's blood cancer cells. This observation has led to more research to learn how immune cells might help us to treat cancer.

This fact sheet provides information about the different types of immunotherapies and their roles in the treatment of blood cancers.

What are immunotherapies?

Immunotherapies are relatively new and promising treatment options for patients with blood cancers. Their development is based on the concept that immune cells or their products, such as antibodies, can be engineered to recognize and kill cancer cells. Monoclonal antibody therapy, donor lymphocyte infusion, vaccine therapy and immune cell-stimulating cytokine therapy are types of immunotherapies that are in use or under study to determine their effectiveness in fighting cancers.

Researchers think that immunotherapies could be less toxic to patients than chemotherapy or radiotherapy. Radiation therapy and most chemotherapy works by damaging the DNA of cancer cells. These therapies generally damage the DNA in normal cells also. This can lead to toxicity or side effects for the patient.

One of the challenges for researchers in developing new and better treatments is to learn more about the differences between cancer cells and normal cells. Cancer cells appear to be composed almost entirely of the same structures as 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 spare normal cells.

Another approach that is being explored by researchers is to find cancer cell structures that are shared only by normal cells of the same type. For example, one current immunotherapy agent, rituximab (Rituxan®), is an approved treatment for B cell lymphoma. The therapy targets lymphoma cells by recognizing a protein on the surface of the lymphoma cell. Rituxan® has a temporary toxic effect on normal B cells because they carry the same target protein. (See *Approved monoclonal antibodies for blood cancer treatment* below for more information about Rituxan®.) However, potentially more serious and longer-lasting toxicities to other normal tissue, such as marrow, lung, liver, heart, and kidney are avoided.

Immunotherapy is likely to be used in combination with, or following, chemotherapy. It is less likely to be used as a single agent for treating established blood cancers. However, immunotherapies may be effective in keeping residual malignant cells in check for prolonged periods in patients treated previously, or simultaneously, with chemotherapy or radiation therapy.

How does the body's immune system work?

To better understand immunotherapies it is helpful to have some basic information about the body's natural immune system.

The immune system helps to maintain our health by protecting us from infectious agents such as bacteria, viruses and fungi. The protection is accomplished by a network of cells that cooperate to identify and disarm “outsiders” - cells or foreign materials that should not be in the body - as compared to “insiders” - cells or products of cells that are normal to the human body.

There are three major branches of the immune system:

- *The antibody-producing branch*, which is composed of white cells, called B lymphocytes (B cells).
 - B cells are specialized cells that recognize markers on the surface of foreign cells (such as bacteria, viruses and fungi) called antigens.
 - B cells mature into plasma cells that secrete antibodies. Antibodies are proteins that coat the invading cell (bacteria, viruses or fungi).
 - Each B cell produces one specific antibody that recognizes one specific cell marker or antigen. The antibody coating is required for other white cells, called neutrophils and monocytes, to ingest and kill the invading cell.

- *The cell-mediated branch*, which is composed of T lymphocytes (T cells) and natural killer cells (NK cells).
 - The T cells have several functions.
 - Helper T cells aid the B cells to make antigen-specific antibodies.
 - Other T cells identify and injure foreign cells directly. These T cells are sometimes referred to as cytotoxic T cells.
 - A natural killer cell is another type of lymphocyte. An NK cell can kill virus-infected cells by attaching to the infected cell and releasing powerful chemicals.
 - Unlike T cells, NK cells can kill a foreign cell without recognizing a specific antigen.
- *The dendritic cell branch*, which is made up of cells derived from the marrow that assist T cells.
 - In order for a T cell to respond to an antigen, the antigen usually must be processed by dendritic cells.
 - The dendritic cells present a specific piece of the antigen to the T cells, resulting in T cell activation.

All cancers begin with a change to the DNA of a single cell. In most circumstances, the immune system cannot identify this changed cell as foreign, an “outsider” to the body, and kill it before it grows into a tumor. One reason the immune system may not see the cancer cell as foreign is that unlike the virus or bacteria cell, there is no unique structural difference between the cancer cell and a normal cell. In addition, we know that cancer suppresses the patient’s immune activity. This factor may also contribute to the immune system’s failure to recognize the cancer cell as foreign.

Certain cancers, such as lymphoma, are more likely to occur in patients whose immune system is depressed by disease or drug therapies. However, for many otherwise healthy people, the cells of the immune system may be functioning normally, yet the changed cell escapes the body’s detection and cancer arises.

What are the types and roles of the various immunotherapies in treating blood cancers?

There are several different types of immunotherapies:

- Monoclonal antibodies.
- Donor lymphocyte infusion.
- Non-myeloablative transplantation.
- Vaccine therapy.
- Immune cell-stimulating cytokines.

Monoclonal Antibodies

Monoclonal antibodies are proteins produced in the laboratory for therapeutic purposes. They are designed to target and destroy cells by recognizing specific structures on the surface of the cell, called antigens. Each monoclonal antibody is designed to bind to a specific antigen on the cancer cell.

Monoclonal antibodies are further classified as *naked*, *radiolabeled*, or *monoclonal antibodies attached to non-radioactive chemicals or toxins*. Naked monoclonal antibodies are those without any drug or radioactive material attached to them. A monoclonal antibody can also be paired with a radioactive substance or a toxic chemical that can kill the target cell. Since the target antigens on malignant cells are usually found on certain normal cells, there is the potential for some toxicity to the normal cells of a closely related type. However, the toxicity is usually tolerable and reversible.

Monoclonal antibody therapy is also known as *passive immunotherapy*. This is distinct from *active immunity* in which a person's own immune cells respond to a foreign invader by making antibodies.

Monoclonal antibodies are administered by intravenous (IV) infusion in a hospital or outpatient setting. Treatments may take up to a few hours and patients are carefully monitored by health care professionals for possible side effects.

Approved monoclonal antibodies for blood cancer treatment

Approved monoclonal antibodies for the treatment of blood cancers include:

Rituximab (Rituxan®) for B cell non-Hodgkin lymphoma. This is a naked monoclonal antibody. It binds to an antigen on B cells called CD20. It is currently approved to treat patients with relapsed or refractory low-grade or follicular, CD20 positive, B cell non-Hodgkin lymphoma.

Alemtuzumab (Campath®) for B cell chronic lymphocytic leukemia (CLL). Campath® is another naked monoclonal antibody, which targets the CD52 antigen found primarily on lymphocytes, monocytes, and NK cells. It is currently approved to treat B cell chronic lymphocytic leukemia (CLL) in patients who have been treated with alkylating agents and who have not responded to fludarabine therapy.

Certain side effects may occur with Rituxan® or Campath®, including fever, shaking, chills, tiredness, headache, and nausea. Other less common but more severe side effects can include: shortness of breath, drop in blood pressure, hypersensitivity, and irregular heartbeat or chest pain.

^{131I}*Tositumomab (Bexxar®) for B cell non-Hodgkin lymphoma*. Bexxar® is a radiolabeled monoclonal antibody, also called radioimmunotherapy. The addition of a radioisotope to the antibody is thought to offer another way to kill a cancer cell, and nearby cancer cells, with minimal toxicity to normal cells. The radioactivity is limited principally to the region around the cancer cells, minimizing radiation effects on normal organs. This agent binds to an antigen on B cells called CD20. It is currently approved to treat patients with CD20 positive follicular non-Hodgkin lymphoma who are resistant to Rituxan® or have relapsed following chemotherapy.

⁹⁰Y *ibritumomab tiuxetan* (*Zevalin*®) for B cell non-Hodgkin lymphoma. Zevalin® is a radiolabeled monoclonal antibody, also called radioimmunotherapy. As with Bexxar® (above), the radioactivity is limited principally to the region around the cancer cells, minimizing radiation effects on normal organs. This agent binds to an antigen on B cells called CD20. It is currently approved for the treatment of adults with relapsed or refractory low-grade follicular or transformed B cell lymphoma.

Bexxar® and Zevalin® may cause the same side effects as naked monoclonal antibodies. In addition, patients may experience lower red cell counts, lower white cell counts and allergic reactions.

Gemtuzumab ozogamicin (*Mylotarg*®) for older adults with relapsed acute myelogenous leukemia (AML). Mylotarg® is an example of a monoclonal antibody attached to a cell toxin (ozogamicin) that acts as a chemotherapy agent. Mylotarg® attaches to the CD33 antigen found on leukemic and certain normal cells. Once attached, the toxin enters the cell and destroys it. Mylotarg® is currently approved to treat patients with CD33 positive AML in first relapse, who are 60 years of age or older and who are not considered candidates for other cytotoxic chemotherapy.

Side effects that may occur with Mylotarg® include: decrease in blood cell production in the marrow resulting in low red cell counts, low blood platelets, swelling of the membrane inside the mouth, liver problems and rash.

Monoclonal antibodies in clinical trials

In addition to their approved uses, these monoclonal antibodies are being tested in clinical trials for other related blood cancers. Clinical trials are experimental studies designed to test a new treatment's safety and effectiveness. For example, Rituxan® may be effective in treating chronic lymphocytic leukemia (CLL), another B cell cancer.

Other examples of monoclonal antibodies being tested in clinical trials include:

- Bevacizumab for chronic myelogenous leukemia (CML) and acute myelogenous leukemia (AML).
- Immunotoxin BL22 for hairy cell leukemia.
- ¹³¹I Antibody BC8 for acute leukemia and myelodysplastic syndrome (MDS).
- Epratuzumab and ⁹⁰Y Epratuzumab for B cell non-Hodgkin lymphoma.

Donor lymphocyte infusion

Donor lymphocyte infusion is another form of immunotherapy. It is approved for use in patients with relapsed chronic myelogenous leukemia (CML), and in younger patients with myeloma following allogeneic stem cell transplantation. (Allogeneic transplants usually use unrelated-matched or related-matched donors.)

The benefit of allogeneic stem cell transplantation for treating blood cancers partly depends on the intensive chemoradiotherapy that is given before stem cell infusion. The purpose of the chemoradiotherapy is to treat the cancer and, to impair the patient's immune system to prevent rejection of the donor cells. In addition, the benefit of allogeneic stem cell transplant depends on the later-effect of the donor lymphocytes (immune cells) to attack the patient's blood cancer cells.

With donor lymphocyte infusion, the patient's immune system has been reconstituted with donor cells as a result of the stem cell transplant. The patient can tolerate the later infusion of donor lymphocytes to some extent. The donor and patient are very similar (but not identical) in tissue type. As a result, the donor lymphocytes may recognize minor histocompatibility antigens on the patient's blood cancer cells as foreign to the body, identifying the cells as a target for attack.

A potential risk of donor lymphocyte infusion is severe graft versus host disease (GVHD). Please refer to the next section, Non-myeloablative stem cell transplantation, for a brief explanation of GVHD.

The procedure for donor lymphocyte infusion involves the collection of lymphocytes from the original stem cell donor. The lymphocytes are infused into the patient immediately or after frozen storage. Collection of donor lymphocytes and infusion of the lymphocytes into the patient can both be done on an outpatient basis. In most patients who are candidates for the procedure, donor lymphocyte infusion has been very effective in re-inducing remission. The most dramatic effects of donor lymphocyte infusion are seen in patients with chronic myelogenous leukemia and myeloma, with lesser effects in other blood cancers such as acute myelogenous leukemia (AML), chronic lymphocytic leukemia (CLL) and lymphoma. However, even with these other blood cancers, effects exist and form the basis for non-myeloablative allogeneic stem cell transplantation.

Non-myeloablative stem cell transplantation

With non-myeloablative allogeneic stem cell transplantation, it appears that the major treatment effect is the result of the donor immune cell attack against the patient's blood cell cancer that leads to remission. This effect is called graft versus malignancy (GVM). The GVM effect does not take place in autologous transplantation (which uses the patient's own stem cells) and syngeneic transplantation (which uses stem cells from an identical twin). In these cases, the recipient's restored immune system does not recognize the remaining cancer cells as being foreign bodies and so does not destroy them.

In non-myeloablative transplantation therapy, patients are given mild or moderate cytotoxic treatments prior to the allogeneic stem cell infusion. Powerful immunosuppressive drugs are also given to prevent rejection of the donor cells. The donor cells gain a foothold and gradually, over many months, dominate the patient's blood and immune systems.

The GVM effect underlying the non-myeloablative transplant procedure is strongest in patients being treated for chronic myelogenous leukemia (CML). Patients with other malignancies also benefit from the GVM effect, but to lesser degrees. Results from the non-myeloablative transplants that have been

performed to date suggest that it may be an appropriate treatment for older patients or those in poor health. However, the risks and benefits of this procedure have not yet been clearly established. One known risk is graft versus host disease (GVHD). GVHD is the result of the immune attack by donor lymphocytes (the graft) against the recipient's tissues (the host). The main organs that can be injured by GVHD are the skin, liver and gastrointestinal tract. The reaction may be minimal or severe and is caused in part by minor histocompatibility antigens. These are not part of the human leukocyte antigen (HLA) matching (done prior to transplant) and cannot be identified prior to transplant. GVHD can also be a factor in donor lymphocyte infusion.

Patients interested in exploring the possibilities of a non-myeloablative transplant should speak to their doctors about whether participating in a clinical trial would be an appropriate step for them.

Vaccine Therapy

Therapeutic vaccines, also known as active immunotherapies, are promising new approaches to engage cells of the immune system to target cancer cells. In contrast to conventional vaccines, the aim of therapeutic vaccines is not to prevent disease but rather treat existing disease. At present, there are several therapeutic vaccines being tested in clinical trials. However, no vaccines have received FDA approval yet for blood cancer treatment.

The strategy behind therapeutic vaccines is to make cancer cells more visible to the immune system. There are two current main approaches to therapeutic vaccine development. The first, which is being used in lymphoid cancers, is to tailor the vaccine to the lymphoma cells obtained from each individual patient. The patient must first undergo a biopsy to remove a sample of his or her lymphoma cells. A "personalized" vaccine that contains that individual's unique tumor-associated proteins is engineered in the laboratory. Personalized vaccines generally take several months to make. However, new methods are being investigated to speed up this process.

Other vaccines do not require a patient biopsy. The vaccine is designed to target the antigens generally found on the type of blood cancer cells being treated. It can be used with any patient who has that blood cancer. For example, a vaccine made against chronic myelogenous leukemia (CML) might be used for any patient with the disease.

There are many different types of vaccines in development. The most progress has been made in therapeutic vaccines for patients with B cell lymphoma, for which large, randomized Phase III clinical trials, the last step before requesting FDA approval of a treatment, are underway. Clinical trials for various types of leukemia and myeloma vaccines are in Phase I or Phase II clinical trials.

Cancer vaccines are generally administered by injection, much like a flu shot. Frequently, in addition to a monthly vaccine, patients receive an immune boosting substance called granulocyte-macrophage colony-stimulating factor or GM-CSF. The purpose of GM-CSF is to help stimulate and recruit dendritic (antigen-presenting) cells.

Most patients receiving cancer vaccines experience some redness, swelling, and discomfort at the site of their injections. Some patients also report low-grade fevers, bone or joint pain, and flu-like symptoms. Generally these side effects subside within a few days after each injection. Allergic reactions are possible.

Because all cancer vaccines are investigational agents, the full extent of side effects may not be known until the large Phase III clinical trials have been evaluated and long-term observation of patients after vaccine approval takes place.

Immune cell-stimulating cytokines

Cytokines are naturally produced biological chemicals that regulate the intensity and duration of immune response. Cytokines also mediate communication between cells. There are many types of cytokines, including natural growth factors and interleukins. Certain cytokines that are identical to natural growth factors and interleukins can also be produced in the laboratory. These are used to treat some types of cancer.

Cytokines used in immunotherapy include:

- Interferons (such as interferon a).
- Interleukins (such as IL-2).
- Colony-stimulating factors, such as GM-CSF or sargramostim (Leukine[®], Prokine[®]) for white cell production.

Interferon a is a protein produced by lymphocytes. It has been shown to inhibit the activity of dividing cancer cells. Very high dose interferon a (produced in the laboratory) acts like a chemotherapeutic agent in blocking cancer cell growth. It is approved for the treatment of chronic myelogenous leukemia (CML) and hairy cell leukemia. It is also widely used in clinical trials for myeloma, non-Hodgkin lymphoma and cutaneous T cell lymphoma.

Interferon a is generally administered every day or several days a week. It is injected under the skin with a needle. However, new formulations of interferon called pegylated interferon are now available with once a week dosing.

The use of interferon a is associated with flu-like side effects: fever, muscle aches and weakness. In some patients, prolonged fatigue and weight loss may require reduction in the number of doses administered. Hair loss, diarrhea, depression, ulceration of the lining of the mouth, cardiac effects and other side effects occasionally occur and may require changes in treatment approaches.

Interleukins are proteins produced by lymphocytes in order to activate other lymphocytes such as cytotoxic T cells and NK cells. One of the interleukins, IL-2, is being studied for use in treating patients with lymphoma and myeloma.

Colony-stimulating factors (CSFs), sometimes referred to as growth factors, stimulate the growth and maturation of young blood cells in the marrow. One growth factor, GM-CSF, also acts to enhance the effectiveness of certain experimental vaccines.

What are the next steps for immunotherapies in the treatment of blood cancers?

Scientists and clinicians are working together to try to determine which patients are most likely to benefit from immunotherapy, how long treatment is needed, and what combinations of therapies are most appropriate for each patient. Clinical trials are currently underway to answer such questions.

Patients interested in immunotherapy clinical trials should talk to their physicians to learn if they are candidates for this type of treatment.

Resources

The Leukemia & Lymphoma Society

The Leukemia & Lymphoma Society is a national voluntary health agency with 68 chapters in the United States and Canada. It provides education and support services for the public and for cancer treatment professionals. To find an LLS chapter nearest you, visit our online chapter finder or contact:

The Leukemia & Lymphoma Society
1311 Mamaroneck Avenue
White Plains, NY 10605
(800) 955-4572 or www.LLS.org

Through LLS's Information Resource Center, callers may speak directly with an Information Specialist, Monday-Friday, 9 a.m. - 6 p.m., ET at (800) 955-4572. To contact an Information Specialist, click on Live Help (10 a.m. - 5 p.m.) on LLS's Web site or email us at 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 and myeloma. LLS's Web site features a link to the clinical trial searching service of the National Cancer Institute.

Clinical trials listings for blood cancers, including abstracts of clinical trial protocols and contact information, are available.

LLS provides fact sheets and booklets that can be ordered via the 800 number or through the Free Materials section on the Web site, www.LLS.org.

Blood and Marrow Stem Cell Transplantation

Understanding Drug Therapy and Managing Side Effects

Understanding Clinical Trials for Blood Cancers

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Biological Therapies: Using the Immune System to Treat Cancer.

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