Fact Sheet

The Leukemia & Lymphoma Society®
Fighting Blood-Related Cancers

Radioimmunotherapy as a Treatment for Lymphoma

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Radioimmunotherapy is a newly approved cancer treatment that combines two types of therapies–*radiation* therapy and immune therapy using *monoclonal antibodies*.

Monoclonal antibodies are immune proteins made in the laboratory to target and attach to a special part (an *antigen*) of the surface of a cell. Radiation-emitting molecules, referred to as *radioisotopes*, can be attached to the monoclonal antibodies. Those monoclonal antibodies targeted to cancer cells can carry the radiation-emitting molecule to the cancer cells, resulting in more localized, target-specific irradiation. Once attached to the surface of the cancer cell, the radioisotope may kill the cancer cells. Some normal cells that share the same antigen might also be killed. Radioimmunotherapy is being studied in several cancers, but has shown the most promise in the treatment of blood cell cancers, such as *leukemia* and *lymphoma*.

Usefulness of Radioimmunotherapy

In most cases, patients may be treated in an out-patient facility. Therapy can be completed quickly, usually in one or two treatments. There are fewer side effects compared to most high dose *chemotherapy* treatments. Targeting limits the toxic effects on normal tissues, although in most cases of leukemia and lymphoma in which this technique is used, the production of blood cells by the bone marrow is decreased for a period of time. This is because the target cells are in the *bone marrow* as well as other sites and thus the marrow receives radiation. The targeting antibodies themselves, may in some cases, have a killing effect on the tumor cell.

Techniques of Immunotherapy

The use of *immunotherapy* that uses immune cells or proteins (antibodies) to treat cancer is still new and the greatest success thus far has been in the treatment of lymphoma.

Words in the glossary are italicized the first time that they appear in the text.

There are three general types of immunotherapy to treat cancer: immune cell therapy, vaccine therapy, and *antibody* therapy. Radioimmunotherapy uses antibody therapy. Immune cell therapy and vaccine therapies are described in the Society's booklets *Blood and Marrow Stem Cell Transplantation* and T*he Lymphomas* and the Society's *Immunotherapy Fact Sheet.*

Antibody–based Immunotherapy for Lymphoma

This type of immunotherapy uses "monoclonal" antibodies to target cancer cells. The term "monoclonal" implies that these antibody proteins, which are made in the laboratory, are very specific for a particular site on the cancer cells.

The first immunotherapy that proved useful in the treatment of leukemia or lymphoma used antibodies against a target on B *lymphocytes.* This target is referred to as "CD20" and the antibodies targeted to it are called "anti–CD20 antibodies." This target is present on the tumor cells in virtually all B cell lymphomas. The use of the anti–CD20 antibodies to treat B cell lymphomas has been the major advance in lymphoma treatment in the past decade. Since the antibody itself is toxic to lymphoma cells, it is considered a "naked" antibody. That is, it has no additional toxic agent attached to it. The antibodies attach to the antigen and result in the death of the cell.

Two approaches have been used to improve the ability of antibody–based immunotherapy to kill cancer cells. One method is to attach a chemical toxin to an antibody. If the antibody carrying the toxin attaches to and is taken up by the cancer cell, the toxin may lead to the cancer cell's death. This approach has been used in the treatment of acute myelogenous leukemia. An antibody directed against a target, CD33, on the myelogenous leukemia cells has been linked to a potent cell toxin. The FDA has approved this antibody–mediated leukemia therapy for certain patients with acute myelogenous leukemia who do not respond to chemotherapy. The second approach to enhance the effect of antibody–mediated therapy is to attach a radioisotope to the antibody. Several types of radioactive elements or radioisotopes have been found to be useful. One uses radioactive yttrium and another uses radioactive iodine to attach to an anti–CD20 antibody.

The Use of Radioimmunotherapy to Treat Lymphoma

Before the treating dose of radioimmunotherapy, the patient will receive preparatory infusions of non–radiation–linked antibody and then low dose radiation–linked antibody. Then radiation–linked anti–CD20 monoclonal antibodies are injected into a vein of the patient. They circulate through the tissues and attach to B lymphoma cells and to normal B lymphocytes. The antibodies bring radioactivity to the lymphoma cells and result in localized killing of the cancer cells (and some normal B lymphocytes).

Radioimmunotherapy Works Differently Than Chemotherapy

Radioimmunotherapy is designed to target specific cancer cells. Chemotherapy, on the other hand, destroys any rapidly dividing cell, which often include non-cancer cells as well as cancer cells. Because the cells of the *immune system*, bone marrow, lining cells of the intestines, skin and hair follicles cells tend to be especially sensitive to the effects of chemotherapy, they are often damaged or destroyed along with the cancer cells. Damage of these non-cancerous cells by intensive chemotherapy may lead to side effects such as a low blood cell counts and risk of infection, mouth ulcers, diarrhea, nausea and vomiting, rashes, and hair loss.

The effects depend on the type, dose, and number of chemotherapeutic agents used. Some of these side effects are not associated with radioimmunotherapy or if they occur, are milder and do not last as long. One organ that is affected by radioimmunotherapy is the bone marrow. The radioactivity attaches to B lymphocytes in the marrow but the neighboring blood cell-forming marrow cells are radiated as well. This leads to decreases in blood cell counts after treatment.

Radioimmunotherapy is usually delivered over a shorter period of time than chemotherapy. Although the length of treatment varies, most patients receive chemotherapy over the course of several months or occasionally longer. In contrast, radioimmunotherapy is usually delivered over a shorter (one to three weeks) period of treatment.

Are Hospitalization and Special Precautions Required?

Treatment is given to the patient in a medical setting that is licensed to use radiation in therapy for cancer. Under most circumstances, patients receive radioimmunotherapy as an outpatient, which means they go to the hospital to be treated but do not have to stay overnight. The therapy can take several hours to complete.

Precautions in the use of radioactive isotopes are related to the type of isotope being given to the patient. In the form of therapy that combines the radioactive isotope yttrium-90 to an antibody to CD20, the radioactivity acts over a very short distance and there are few special precautions after it is given to the patient. This agent, ibritumomab tiuxetan (Zevalin®), has been approved by the FDA for use in certain patients with B cell lymphoma.

In the form of treatment that couples radioactive iodine with the antibody to CD20 tositumomab (Bexxar®), care has to be taken for several days to minimize exposure of other persons who may come in contact with the patient. The radioactive isotopes

"decay," that is they change from radioactive to non-radioactive over varying periods of time depending on the isotope. In addition, following treatment, the radioactive particles are excreted in bowel movements, urine and other body fluids. During this time, the doctor and nurse should explain to you what precautions are required in order to protect other people from exposure to the radiation. The precautions needed and the length of time they are needed varies with the radioactive isotope used.

How will the Doctor Know if it is Working?

Radioimmunotherapy works gradually, and it may take several months for cancer cells to die and tumors to shrink. In order to measure this progress, your doctor will keep track of lymph node areas that can be felt and use imaging studies (CT Scan, MRI, nuclear medicine scans, etc.) for more deeply placed lymphoma masses.

Will there be Side Effects?

As with every type of cancer treatment, radioimmunotherapy is associated with some side effects. Occasionally patients may have a severe reaction to the preparatory infusions. This and other risks should be discussed with the patient's doctor.

Fever, chills, and aches can occur after the treatment is given. Patients may be given drugs to reduce these effects. Some patients have nausea and vomit, but not as much or for as long as when given chemotherapy. Anti-nausea drugs can help prevent this reaction. Patients are also given iodides prior to receiving radioactive iodine linked antibodies. This prevents the radioactive iodine from being taken up the thyroid gland. The thyroid gland normally concentrates iodide because it is used to make thyroid hormone.

The most common side effect of radioimmunotherapy is a reduction in blood counts caused by the radiation of the bone marrow. There are three main cellular components of blood–*red cells*, *white cells*, and *platelets*–and each type performs specific duties:

- white cells fight infection–a very severe reduction can limit the body's ability to fight infections caused by bacteria, viruses, funguses, or other pathogens
- red cells carry oxygen–a reduction in red cells is called *anemia*
- platelets assist in the clotting process–a severe reduction can result in abnormal bruising and bleeding

For most patients, a reduction in blood counts is usually mild to moderate and are not lasting. Other reactions include low blood pressure, diarrhea, or rash. Rash or swelling at the site of the injection affects some patients. These reactions tend to be mild to moderate and are short-lived.

The side effects of this form of therapy will be influenced in part by whether the patient has had chemotherapy and/or *external radiotherapy* before receiving radioimmunotherapy. These previous treatments may increase the frequency and severity of low blood counts after radioimmunotherapy.

When is Radioimmunotherapy an Option for Treating Lymphoma?

Radioimmunotherapy has now been added as a treatment choice for *relapsed* or *refractory* B cell lymphoma. Treatment choices when lymphoma is first diagnosed depend on the cell type, extent of disease and the rate of progression. Management ranges from watch and wait, external radiation, chemotherapy, and/or monoclonal antibody therapy. These therapies can be given either alone or in combination. Some patients may require very high–dose chemotherapy and/or, external radiation followed by *stem cell transplantation* for treatment. Radioimmunotherapy is currently used for those patients whose disease does not respond to initial treatments.

What Types of Radioimmunotherapy are Available?

Currently there are two radioimmunotherapy agents available which have received Food and Drug Administration (FDA) approval.

Ibritumomab tiuxetan (Zevalin®), which was developed by IDEC Pharmaceutical Corporation in San Diego, California and was approved by the FDA in March 2002. Zevalin is indicated for the treatment of adults with relapsed or refractory low–grade, follicular, or transformed B–cell lymphoma; its safety has not been determined in children.

Tositiumomab (Bexxar®), was developed by Corixa and GlaxoSmithKline was approved by the FDA in June 2003. Bexxar is indicated for the treatment of patients with CD20 positive, follicular, non-Hodgkin lymphoma who are resistant to Rituxan® (rituximab) and have relapsed following chemotherapy

Radioimmunotherapy is being studied as a therapy for newly diagnosed lymphoma and to treat cancers other than lymphoma. For more information about *clinical trials* for lymphoma, contact The Leukemia & Lymphoma Society @ 1-800-955-4572 or at www.LLS.org.

This publication is designed to provide accurate and authoritative information in regard to the subject matter covered. It is distributed as a public service by The Leukemia & Lymphoma Society, with the understanding that The Leukemia & Lymphoma Society is not engaged in rendering medical or other professional services.

Additional Reading

The Lymphomas. The Leukemia & Lymphoma Society, 2004.

Blood and Marrow Stem Cell Transplantation, The Leukemia & Lymphoma Society, 2002.

Online Glossary at www.LLS.org

Cancer Clinical Trials Fact Sheet. The Leukemia & Lymphoma Society, 2003.

Glossary of Terms

ANEMIA – A decrease in hemoglobin content of the blood. The hemoglobin concentration determines the oxygen carrying capacity of blood.

ANTIBODY – A protein made by plasma cells (a type of B lymphocyte) in response to a foreign particle such as a bacterium, virus, inhaled pollen, ingested food, or a drug.

ANTIGEN – Any portion of a foreign particle that is recognized by the cells of the immune system to which an antibody is made. Common antigens introduced into the body by bacteria, viruses, pollen, foods, and drugs.

BONE MARROW – Spongy tissue in the center of bones in which blood cells are made and from which they are released into the blood.

CHEMOTHERAPY – The use of chemicals (drugs) to kill cancer cells.

CLINICAL TRIAL – A carefully planned study of a new drug or treatment approach or a new application of an existing drug or approach. Usually, a trial compares the new approach to an existing approach to learn if it is better and less toxic.

EXTERNAL RADIATION – Radiation that is delivered from a device (machine) and penetrates into the patient. It is aimed at unwanted tissue such as a cancer.

IMMUNE SYSTEM – The body's defense system principally against infection. It is composed of cells, especially lymphocytes and of special structures, including lymph nodes.

IMMUNOTHERAPY – A term applied to treatments that use immune cells or products of immune cells to combat disease. It ranges from allergy desensitizing injections to experimental vaccines to fight cancer.

LEUKEMIA – A cancer that originates in a bone marrow cell.

LYMPHOCYTE – A type of white blood cell that is the essential cell type in the body's immune system. There are three major types of lymphocytes: B lymphocytes that produce antibodies to help combat infectious agents like bacteria, viruses and fungi; T lymphocytes that have several functions, including assisting B lymphocytes to make antibodies, and natural killer (NK) cells that can attack virus-infected cells or tumor cells.

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LYMPHOMA – A cancer that originates in a lymphocyte.

MONOCLONAL ANTIBODIES – Antibodies that are produced in the laboratory that are targeted top a very specific antigen. Although previously used principally for diagnostic tests and research, they have recently been applied to disease treatment.

PLATELETS – A blood cell about one tenth the size of a red cell that fosters blood clotting at the site of blood vessel injury.

RADIATION – A type of energy that may take the form of X-rays, gamma rays, beta rays, or alpha rays. X-rays are used to image tissues such as in diagnostic X-rays or at higher intensity to treat certain diseases, especially cancers. Isotopes of elements that emit alpha, beta, or gamma rays can be used in medical diagnosis, research, or in some cases to treat disease especially cancer. Radioimmunotherapy uses isotopes in cancer treatment.

RADIOISOTOPES – Different forms of the same element. One form may emit sufficient radioactivity to be useful in medical diagnosis or treatment.

RED CELLS – Blood cells that are filled with hemoglobin; also known as erythrocytes. Oxygen binds reversibly to hemoglobin. Red cells pick up oxygen in the lungs and deliver oxygen to the tissues. Hemoglobin is a red pigment giving the cells their color and name.

REFRACTORY – The ability of cells to live and divide despite their exposure to a drug that ordinarily kills or slows their growth.

RELAPSE – A return of the disease after it has been in remission following treatment.

STEM CELL TRANSPLANTATION (from blood or marrow) – Stem cells are the parent cells of blood and immune cells. In circumstances in which the marrow is unable to produce blood cells as a result of disease or injury, stem cells may be obtained from a healthy donor matched for tissue type and used to restore blood cell production of a recipient (patient).

WHITE BLOOD CELLS – Also called leukocytes. The five major types of white blood cells are neutrophils, eosinophils, basophils, monocytes, and lymphocytes. Neutrophils, monocytes, and lymphocytes cooperate to fight many types of infections (e.g., bacterial, viral, fungal).

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