Biological Therapies for Cancer:
Questions and Answers

KEY POINTS

- Biological therapies use the body's immune system to fight cancer or to lessen the side effects that may be caused by some cancer treatments.
- Biological response modifiers (BRM's) occur naturally in the body. They can be produced in the laboratory. BRM's alter the interaction between the body's immune defenses and cancer cells to boost, direct, or restore the body's ability to fight the disease.
- Biological therapies include:
  - Interferons.
  - Interleukins.
  - Colony-stimulating factors.
  - Monoclonal antibodies.
  - Vaccines.
  - Gene therapy.
  - Nonspecific immunomodulating agents.
- Biological therapies can cause a number of side effects. They can vary widely from agent to agent and patient to patient.

WHAT IS BIOLOGICAL THERAPY?

Biological therapy is sometimes called immunotherapy, biotherapy, or biological response modifier therapy. It is a relatively new addition to the family of cancer treatments. It also includes surgery, chemotherapy, and radiation therapy. Biological therapies use the body's immune system, either directly or indirectly, to:

- Fight cancer.
- Lessen the side effects that may be caused by some cancer treatments.

WHAT IS THE IMMUNE SYSTEM AND WHAT ARE ITS COMPONENTS?

The immune system is a complex network of cells and organs. They work together to defend the body against attacks by “foreign” or “non-self” invaders. This network is one of the body's main defenses against infection and disease. The immune system works against diseases, including cancer, in a variety of ways. For example, the immune system may recognize the difference between healthy cells and cancer cells in the body. It works to eliminate cancerous cells. But the immune system does not always recognize cancer cells as “foreign.” Also, cancer may develop when the immune system breaks down or does not function adequately. Biological therapies are designed to repair, stimulate, or enhance the immune system's responses.

Immune system cells include the following:

- Lymphocytes are a type of white blood cell found in the blood and many other parts of the body. Types of lymphocytes include:
  - B cells.
  - T cells.
  - Natural Killer cells.

B cells (B lymphocytes) mature into plasma cells that secrete proteins called antibodies (immunoglobulins). Antibodies recognize and attach to foreign substances known as antigens. They fit together much the way that a key fits a lock. Each type of B cell makes one specific antibody. That antibody recognizes one specific antigen.

- T cells (T lymphocytes) work primarily by producing proteins called cytokines. Cytokines allow immune system cells to communicate with each other. They include:
  - Lymphokines.
  - Interferons.
  - Interleukins.
  - Colony-stimulating factors.
- Some T cells, called cytotoxic T cells, release pore-forming proteins. They directly attack infected, foreign, or cancerous cells. Other T cells, called helper T cells, regulate the immune response by releasing cytokines to signal other immune system defenders.

WHAT ARE BIOLOGICAL RESPONSE MODIFIERS, AND HOW CAN THEY BE USED TO TREAT CANCER?

Some antibodies, cytokines, and other immune system substances can be produced in the lab for use in cancer treatment. These substances are often called biological response modifiers (BRM's). They alter the interaction between the body's immune defenses and cancer cells. This is to boost, direct, or restore the body's ability to fight the disease. BRM's include:

- Interferons.
- Interleukins.
- Colony-stimulating factors.
- Monoclonal antibodies.
- Vaccines.
- Gene therapy.
- Nonspecific immunomodulating agents.

Researchers continue to discover new BRM's, to learn more about how they function, and to develop ways to use them in cancer therapy. Biological therapies may be used to:

- Stop, control, or suppress processes that permit cancer growth.
- Make cancer cells more recognizable and, therefore, more susceptible to destruction by the immune system.
- Boost the killing power of immune system cells, such as T cells, NK cells, and macrophages.
- Alter the growth patterns of cancer cells to promote behavior like that of healthy cells.
- Block or reverse the process that changes a normal cell or a precancerous cell into a cancerous cell.
- Enhance the body's ability to repair or replace normal cells damaged or destroyed by other forms of cancer treatment, such as chemotherapy or radiation.
- Prevent cancer cells from spreading to other parts of the body.

Some BRM's are a standard part of treatment for certain types of cancer. Others are being studied in clinical trials (research studies). BRM's are being used alone or in combination with each other. They are also being used with other treatments. These include radiation therapy and chemotherapy.

WHAT ARE INTERFERONS?

Interferons (IFN's) are types of cytokines that occur naturally in the body. They were the first cytokines produced in the laboratory for use as BRM's. There are three major types of interferons. They are:

- Interferon alpha.
- Interferon beta.
- Interferon gamma.

Interferon alpha is the type most widely used in cancer treatment.

Researchers have found that interferons can improve the way a cancer patient's immune system acts against cancer cells. Also, interferons may act directly on cancer cells. They do this by slowing their growth or promoting their development into cells with more normal behavior. Researchers believe that some interferons may also stimulate NK cells, T cells, and macrophages. This boosts the immune system's anticancer function.

The U.S. Food and Drug Administration (FDA) has approved the use of interferon alpha for the treatment of certain types of cancer. These include:

- Hairy cell leukemia.
- Melanoma.
- Chronic myeloid leukemia.
- AIDS-related Kaposi's sarcoma.

Studies have shown that interferon alpha may also be effective in treating other cancers such as kidney cancer and non-Hodgkin's lymphoma. Researchers are exploring combinations of interferon alpha and other BRM's or chemotherapy in clinical trials to treat a number of cancers.

WHAT ARE INTERLEUKINS?

Like interferons, interleukins (IL's) are cytokines. They occur naturally in the body and can be made in the lab. Many interleukins have been identified. But interleukin-2 (IL2 or aldesleukin) has been the most widely studied

in cancer treatment. IL2 stimulates the growth and activity of many immune cells, such as lymphocytes, that can destroy cancer cells. The FDA has approved IL2 for the treatment of metastatic kidney cancer and metastatic melanoma.

Researchers continue to study the benefits of interleukins to treat a number of other cancers. These include:

- Leukemia.
- Lymphoma.
- Brain, colorectal, ovarian, breast, and prostate cancers.

WHAT ARE COLONY-STIMULATING FACTORS?

Colony-stimulating factors (CSF's) are sometimes called hematopoietic growth factors. They usually do not directly affect tumor cells. Rather, they encourage bone marrow stem cells to divide and develop into:

- White blood cells.
- Platelets.
- Red blood cells.

Bone marrow is critical to the body's immune system. It is the source of all blood cells.

Stimulation of the immune system by CSF's may benefit patients undergoing cancer treatment. Anticancer drugs can damage the body's ability to make white blood cells, red blood cells, and platelets. So patients receiving anticancer drugs have an increased risk of:

- Developing infections.
- Becoming anemic.
- Bleeding more easily.

By using CSF's to stimulate blood cell production, doctors can increase the doses of anticancer drugs without increasing the risk of infection or the need for transfusion with blood products. So researchers have found CSF's particularly useful when combined with high-dose chemotherapy.

Some examples of CSF's and their use in cancer therapy are as follows:

- GCSF (filgrastim) and GMCSF (sargramostim) can increase the number of white blood cells. This reduces the risk of infection in patients receiving chemotherapy. GCSF and GMCSF can also stimulate the production of stem cells in preparation for stem cell or bone marrow transplants.
- Erythropoietin (epoetin) can increase the number of red blood cells. It reduces the need for red blood cell transfusions in patients receiving chemotherapy.
- Interleukin-11 (oprelvekin) helps the body make platelets. It can reduce the need for platelet transfusions in patients receiving chemotherapy.
- Researchers are studying CSF's in clinical trials to treat a large variety of cancers. These include:
  - Lymphoma.
  - Leukemia.
  - Multiple myeloma.
  - Melanoma.
  - Cancers of the brain, lung, esophagus, breast, uterus, ovary, prostate, kidney, colon, and rectum.

WHAT ARE MONOCLONAL ANTIBODIES?

Researchers are evaluating the effectiveness of certain antibodies made in the lab. They are called monoclonal antibodies (MOAB's or MoAB's). These antibodies are produced by a single type of cell. They are specific for a particular antigen. Researchers are examining ways to create MOAB's specific to the antigens found on the surface of various cancer cells.

To create MOAB's , scientists first inject human cancer cells into mice. In response, the mouse immune system makes antibodies against these cancer cells. The scientists then remove the mouse plasma cells that produce antibodies. They fuse them with laboratory-grown cells to create “hybrid” cells. They are called hybridomas. Hybridomas can indefinitely produce large quantities of these pure antibodies, or MOAB's.

- MOAB's may be used in cancer treatment in a number of ways:
- MOAB's that react with specific types of cancer may enhance a patient's immune response to the cancer.
- MOAB's can be programmed to act against cell growth factors. This interferes with the growth of cancer cells.

- MOAB's may be linked to anticancer drugs, radioisotopes (radioactive substances), other BRM's, or other toxins. When the antibodies latch onto cancer cells, they deliver these poisons directly to the tumor. This helps to destroy it.
- MOAB's carrying radioisotopes may also prove useful in diagnosing certain cancers, such as colorectal, ovarian, and prostate.

Rituxan® (rituximab) and Herceptin® (trastuzumab) are examples of MOAB's that have been approved by the FDA. Rituxan is used for the treatment of non-Hodgkin's lymphoma. Herceptin is used to treat metastatic breast cancer in patients with tumors that produce excess amounts of a protein called HER2. (More information about Herceptin is available in the National Cancer Institute (NCI) fact sheet Herceptin® (Trastuzumab): Questions and Answers, which can be found at http://www.cancer.gov/cancertopics/factsheet/Therapy/herceptin on the Internet.) In clinical trials, researchers are testing MOAB's to treat lymphoma, leukemia, melanoma, and cancers of the brain, breast, lung, kidney, colon, rectum, ovary, prostate, and other areas.

WHAT ARE CANCER VACCINES?

Cancer vaccines are another form of biological therapy currently under study. Vaccines for infectious diseases, such as measles, mumps, and tetanus, are injected into a person before the disease develops. These vaccines are effective because they expose the body's immune cells to weakened forms of antigens that are present on the surface of the infectious agent. This exposure causes the immune system to increase production of plasma cells that make antibodies specific to the infectious agent. The immune system also increases production of T cells that recognize the infectious agent. These activated immune cells remember the exposure. So the next time the agent enters the body, the immune system is already prepared to respond and stop the infection.
Researchers are developing vaccines that may encourage the patient's immune system to recognize cancer cells. Cancer vaccines are designed to treat existing cancers (therapeutic vaccines) or to prevent the development of cancer (prophylactic vaccines). Therapeutic vaccines are injected in a person after cancer is diagnosed. These vaccines may:

- Stop the growth of existing tumors.
- Prevent cancer from recurring.
- Eliminate cancer cells not killed by prior treatments.

Cancer vaccines given when the tumor is small may be able to destroy the cancer. On the other hand, prophylactic vaccines are given to healthy individuals before cancer develops. These vaccines are designed to stimulate the immune system to attack viruses that can cause cancer. By targeting these cancer-causing viruses, doctors hope to prevent the development of certain cancers.
Early cancer vaccine clinical trials involved mainly patients with melanoma. Therapeutic vaccines are also being studied in the treatment of many other types of cancer. These include lymphoma, leukemia, and cancers of the brain, breast, lung, kidney, ovary, prostate, pancreas, colon, and rectum. Researchers are also studying prophylactic vaccines to prevent cancers of the cervix and liver. Moreover, scientists are investigating ways that cancer vaccines can be used in combination with other BRM's.

WHAT IS GENE THERAPY?

Gene therapy is an experimental treatment that involves introducing genetic material into a person's cells to fight disease. Researchers are studying gene therapy methods that can improve a patient's immune response to cancer. For example, a gene may be inserted into an immune cell to enhance its ability to recognize and attack cancer cells. In another approach, scientists inject cancer cells with genes that cause the cancer cells to produce cytokines. This will stimulate the immune system. A number of clinical trials are currently studying gene therapy and its potential application to the biological treatment of cancer. (More information about gene therapy is available in the NCI fact sheet Gene Therapy for Cancer: Questions and Answers, which can be found at http://www.cancer.gov/cancertopics/factsheet/Therapy/gene on the Internet.)

WHAT ARE NONSPECIFIC IMMUNOMODULATING AGENTS?

Nonspecific immunomodulating agents are substances that stimulate or indirectly augment the immune system. Often, these agents target key immune system cells. And they cause secondary responses such as increased

production of cytokines and immunoglobulins. Two nonspecific immunomodulating agents used in cancer treatment are:

- Bacillus Calmette-Guerin (BCG).
- Levamisole.

BCG has been widely used as a tuberculosis vaccine. It is used in the treatment of superficial bladder cancer following surgery. BCG may work by stimulating an inflammatory, and possibly an immune, response. A solution of BCG is instilled in the bladder. It stays there for about 2 hours before the patient is allowed to empty the bladder by urinating. This treatment is usually performed once a week for 6 weeks.

Levamisole is sometimes used along with fluorouracil (5FU) chemotherapy in the treatment of stage III (Dukes' C) colon cancer following surgery. Levamisole may act to restore depressed immune function.

DO BIOLOGICAL THERAPIES HAVE ANY SIDE EFFECTS?

Like other forms of cancer treatment, biological therapies can cause a number of side effects. These can vary widely from agent to agent and patient to patient.

BRM side effects may include:

- Rashes or swelling at the site where the BRM's are injected.
- Flu-like symptoms including:
  - Fever.
  - Chills.
  - Nausea.
  - Vomiting.
  - Appetite loss.
- Fatigue.
- Blood pressure changes.
- The side effects of IL2 can often be severe. It depends upon the dosage given. Patients need to be closely monitored during treatment with high doses of IL2.
- Side effects of CSF's may include:
  - Bone pain.
  - Fatigue.
  - Fever.
  - Appetite loss.
- The side effects of MOAB's vary. Serious allergic reactions may occur.
- Cancer vaccines can cause muscle aches and fever.

WHERE CAN A PERSON GET MORE INFORMATION ABOUT CLINICAL TRIALS?

Information about ongoing clinical trials involving these and other biological therapies is available from the Cancer Information Service (see below) or the clinical trials page of the NCI's Web site at http://www.cancer.gov/clinicaltrials/ on the Internet.

RELATED RESOURCES

Publications (available at http://www.cancer.gov/publications)

- National Cancer Institute Fact Sheet 7.18, Gene Therapy for Cancer: Questions and Answers
- National Cancer Institute Fact Sheet 7.45, Herceptin® (Trastuzumab): Questions and Answers
- National Cancer Institute Fact Sheet 7.46, Access to Investigational Drugs: Questions and Answers
- Biological Therapy: Treatments That Use Your Immune System To Fight Cancer
- Taking Part in Clinical Trials: What Cancer Patients Need To Know
- What You Need To Know About™ Cancer

National Cancer Institute (NCI) Resources
Cancer Information Service (toll-free)
Telephone: 18004CANCER (18004226237)
TTY: 18003328615
Online: NCI's Web site: http://www.cancer.gov
LiveHelp, NCI's live online assistance: https://cissecure.nci.nih.gov/livehelp/welcome.asp

This information is courtesy of the National Cancer Institute branch of the National Institute of Health

Document Released: 11/20/2006 Document Re-Released: 03/16/2010
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