

Review

Biological Response Modifiers Used in Cancer Biotherapy

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Abstract. *Biotherapy is a form of treatment that uses the natural immune system to protect the body against infection, cancer, and other diseases, and can fortify the body against some side-effects of other treatments. Biotherapy employs substances called biological response modifiers (BRMs), which include vaccines, monoclonal antibodies, cytokines, and adjuvants. BRMs are used alone or in combination with each other. Several BRMs are widely accepted in the treatment of certain types of cancer, while others are being tried in research studies. Side-effects of biotherapy vary among agents and patients. However, these side-effects usually disappear after the end of treatment.*

Biotherapy, often called biological therapy or immunotherapy, aims at supporting and helping in the treatment of human diseases without chemical drugs and invasive therapies, by restoring the natural immune system (1). It is also used to reduce certain side-effects that may be caused by some treatments against cancer, autoimmune diseases, or other diseases. Biotherapy employs substances called biological response modifiers (BRMs). BRMs, also referred to as biologics (2), are substances that modulate the immune system by stimulating or replacing the function of one or more of the system's components, and the term BRM is often used synonymously with the terms immunomodulator and

immunostimulant (3). BRMs used in biotherapy are usually categorized into two groups (4). The first group consists of specific BRMs, such as vaccines and monoclonal antibodies (MAbs) that provide antigen-specific immune response or activity, and may exhibit a direct antitumor effect. The second group comprises of non-specific BRMs, such as cytokines and adjuvants, which augment or stimulate the immune system without antigenic specificity. Some non-specific BRMs, e.g. cytokines, are normally produced at low levels in the body in response to inflammation, cancer and other diseases. As part of the overall procedure, however, these two kinds of BRMs are sometimes used in combination with each other (1). In addition, using modern laboratory techniques, including hybridoma and genetic engineering technologies, large amounts of BRMs can be produced for use in the treatment of cancer, as well as of other diseases, such as rheumatoid arthritis and Crohn's disease. In this short review, we focus on major BRMs currently used or being tried in cancer therapy.

Vaccines

Vaccines are the most commonly tried BRMs in terms of immunostimulatory substances used in the general human population. Vaccines were originally used to stimulate a protective immune response to specific pathogens. The influenza vaccine, for example, uses several antigens extracted from different strains of the influenza virus. People who are vaccinated are then protected against infection from the corresponding pathogenic viral strains. Some cancer vaccines are designed to work in the same way. For instance, new vaccines, such as Cervarix[®] and Gardasil[®], against the human papilloma virus help prevent cervical, vaginal, vulvar, and anal cancer (5). These vaccines, however, do not target cancer cells themselves but target certain viruses that cause these types of cancer.

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True cancer vaccines include tumor cells, parts of tumor cells, or purified tumor antigens. The vaccines increase the immune response toward tumor cells already existing in the body, and are specific for cancer because they should only bind to, and attack tumor cells. Until now, only one true cancer vaccine, sipuleucel-T (Provenge[®]), has been approved by the U.S. Food and Drug Administration (FDA), and is used in treating advanced prostate cancer (6). For the preparation of this vaccine, white blood cells are collected from the patient's blood and are exposed to a protein, called prostatic acid phosphatase, purified from prostate cancer cells. These cells are then transferred back into the patient by intravenous injection. In the body, the cells can attack the patient's prostate cancer. When used in men with metastatic prostate cancer that no longer respond to hormone therapy, the vaccine helps them live more than four months longer, on average (7). Several different types of other cancer vaccines, including dendritic cell vaccines, are now being studied and are reaching late stage clinical trials (8).

MABs

Although autoantibodies to tumor antigens have been identified in the sera of cancer patients, it is well known that the attack of autoantibodies to tumor antigens is not usually sufficient to completely protect the body. Consequently, we have depended on the power of MABs, which are heteroantibodies against human tumor antigens. MABs are also used to treat some autoimmune diseases. For example, infliximab (Remicade[®]) and adalimumab (Humira[®]) are effective in rheumatoid arthritis, Crohn's disease, and ulcerative colitis, through their inhibitory activity against tumor necrosis factor- α (TNF- α) (9, 10). In cancer therapy, MABs that can distinguish the antigens that are found on tumor cells or can recognize the substances on tumor cells that help tumor cells grow, are exploited (11). The antibodies attach to the substances and kill the tumor cells, block their growth, or keep them from metastasizing. MABs for cancer therapy are also used in combination with chemotherapy. Moreover, they may be used to carry drugs, toxins, or radioisotopes, cytokines or other active conjugates directly to tumor cells (11, 12). Although every native antibody can bind to cell receptors with its Fc region, it is also possible to design bi-specific antibodies that can bind with their Fab regions, both to a target antigen and to a conjugate or immune effector cell (13).

At present time, there are 11 MABs for cancer therapy approved by the FDA and these include bevacizumab (Avastin[®]), cetuximab (Erbix[®]), panitumumab (Vectibix[®]), rituximab (Rituxan[®]), and trastuzumab (Herceptin[®]) (14, 15). Bevacizumab is a humanized MAB that specifically reacts with vascular endothelial growth factor, and is used in the treatment of metastatic colorectal cancer (16), non-small cell lung cancer, glioblastoma, and metastatic renal cell

cancer. Cetuximab is a human-mouse chimeric MAB directed against epidermal growth factor receptor (EGFR), and is approved for colorectal cancer, and head and neck cancer (17). Panitumumab is a fully human MAB that selectively binds to EGFR, and is authorized for the treatment of metastatic colorectal cancer. Rituximab is a chimeric MAB specific to CD20, which is primarily found on the surface of B-cells, and is allowed for use in the treatment of many types of lymphoma and leukemia. Trastuzumab is a humanized MAB against human EGFR2, and is accepted for use against metastatic breast cancer (18). Researchers are still examining ways to generate new MABs specific to the antigens or substances found on the surface of tumor cells, and are testing MABs to treat lymphoma, leukemia, melanoma, and cancer of the brain, lung, breast, kidney, ovary, prostate, colon, rectum, and other organs (19).

Cytokines

Cytokines are a large family of more than 100 proteins and glycoproteins produced by immune cells. They exhibit autocrine and/or paracrine functions, so that they work locally or at a distance to enhance or suppress immune response (20). They function as short-range mediators involved in many biological processes, from cell proliferation and differentiation to immunity, repair, angiogenesis, fibrosis, inflammation, and tumorigenesis (21). As cytokines and their associated receptors provide key signals for important processes, it is not surprising that abnormalities in cytokines, their receptors, and the signaling pathways initiated by them are involved in a wide variety of diseases. Hence, cytokines are often used for the treatment of various diseases (15). In cancer therapy, cytokines are usually used to enhance immunity. Vaccines or other agents that modulate the immune system also rely on cytokine activity. Major cytokines used for cancer therapy are interleukins (ILs), interferons (IFNs), and colony-stimulating factors (CSFs), which have shown promise as cancer therapies.

IL-2 acts indirectly on tumor cells by stimulating T- and B-lymphocytes to kill tumor cells. Recombinant IL-2 (Aldesleukin[®] or Proleukin[®]) is approved for treating metastatic kidney cancer and metastatic melanoma (15, 20).

IFNs interfere with the division of tumor cells and can slow tumor growth; and they also promote normal cell activity and stimulate the body's natural immune system to fight tumor cells. The FDA has approved INF- α -2b (Intron-A[®], Roferon-A[®], *etc.*), a form of INF- α that is made in the laboratory, for the treatment of melanoma, hairy cell leukemia, and AIDS-related Kaposi's sarcoma (2, 20).

CSFs stimulate the bone marrow to produce blood cells. Therefore, CSFs are usually used to increase the number of hematopoietic stem cells in the donor's blood before collection by leukapheresis for use in hematopoietic stem

cell transplantation (22). CSFs have no direct effect on tumor cells. Cancer chemotherapy often causes myelosuppression and unacceptably low levels of white blood cells, increasing the patient's risk for infection and anemia. By stimulating the production of blood cells, CSFs help patients tolerate higher doses of chemotherapy. In particular, granulocyte CSF (G-CSF) stimulates the production of neutrophils. A recombinant form of G-CSF, also called filgrastim (Neupogen[®]) and lenograstim (Neutrogen[®]), is used for certain cancer patients, such as those with leukemia, lymphoma and breast cancer, to accelerate the speed of recovery from neutropenia after chemotherapy (23).

Adjuvants

Adjuvants are substances that non-specifically stimulate or indirectly augment the immune system. They are often included in vaccines or are used with drugs to enhance the recipient's immune response to a supplied antigen, while allowing for the injected foreign material to be kept to a minimum. In cancer therapy, however, several adjuvants are sometimes used independently of the vaccine to non-specifically activate the immune response, on the assumption that the patient's tumor cells possess the tumor-specific antigen. Such adjuvants include bacillus Calmette-Guerin (BCG), polysaccharide-Kureha (PS-K), and streptococcal preparation OK-432 (OK-432), *etc.* Some immunostimulatory nutrients are also used as adjuvants for cancer therapy.

BCG has been widely used as a tuberculosis vaccine. Freeze-dried BCG, such as Immunobladder[®] and ImmuCyst[®], is used in the treatment of superficial bladder cancer following surgery (24). BCG may act by stimulating an inflammatory, and, possibly, an immune response. A solution of BCG is instilled in the bladder and maintained there for a few hours before the patient is allowed to empty the bladder by urinating.

PS-K (Krestin[®]) is a protein-bound polysaccharide isolated from the mushroom *Trametes versicolor* and is given to the patients by oral administration. This is used as an immunostimulatory agent in the treatment of gastric and colorectal cancer in some countries in Europe as well as in China and Japan (25). In Japan, PS-K is approved as an adjuvant for cancer chemotherapy following surgery.

OK-432 (Picibanil[®]), a lyophilized preparation of a low-virulence strain of *Streptococcus pyogenes*, has also been approved in Japan as an adjuvant for cancer chemotherapy following surgery. OK-432 has been reported to induce various cytokines, activate immunological cells and thus augment antitumor immunity, and is reported to be effective for gastric cancer, lung cancer, and head and neck cancer (26).

One of the immunostimulatory nutrients is β -glucan, which is a polysaccharide of D-glucose monomers linked by β -glycosidic bonds. Various types of β -glucans occur in cellulose fibers in trees and plants, and can also be found in

yeast, bacteria, and fungi (27). They have been tested as adjuvants in cancer therapy, as well as in the treatment of certain types of allergy. Most of the available evidence comes from pre-clinical data, but firm conclusions on their clinical importance have not yet been reached (28).

Although many researchers are still looking for immunostimulatory nutrients to treat cancer, it is important to find substances which are not degraded or damaged in the digestive tract and can be absorbed as their active forms, if they are to be used by oral administration (26).

Side-effects of Biotherapy

Like other forms of cancer treatment, biotherapies using BRMs also cause some side-effects, depending on the type of treatment. However, these gradually subside after treatment stops.

Common side-effects of a cancer vaccine, such as those occurring with the use of sipuleucel-T, include muscle ache, fever, chills, fatigue, back and joint pain, nausea, and headache (29); a few men may have more severe symptoms, including breathing problems and high blood pressure, which improve with treatment progression.

The side-effects of MAbs vary, and serious allergic reactions may occur. One of the significant complications of trastuzumab is its effect on the heart (30). Some patients are unable to tolerate this drug because of pre-existing heart problems. The risk of cardiomyopathy is increased when trastuzumab is combined with anthracycline chemotherapy, which by itself is associated with cardiac toxicity.

Although cytokines are naturally occurring proteins, they may still cause side-effects. The most common side-effects are reactions at the injection site and flu-like symptoms, such as fever, chills, fatigue, nausea, vomiting, and appetite loss. In addition, IL-2 may cause rashes or swelling, and higher doses may result in low blood pressure, blood and kidney toxicities, and pulmonary edema (31). These can often be severe, depending on the administered dose. Patients need to be carefully monitored during treatment with high doses of IL-2. IFN- α may cause depression and decreased energy (32), and side-effects of CSFs may include bone pain (33).

Adjuvants sometimes cause side-effects, which also include flu-like symptoms, such as chills, fever, weakness, muscle ache, appetite loss, nausea, vomiting, and diarrhea (34). However, these side-effects are usually short-termed and easily improve after treatment ends.

Summary

We have summarized BRMs used for the current biotherapeutic approaches against cancer. Many BRMs, such as vaccines, antibodies, and cytokines, can now be produced in the laboratory for use in cancer treatment. They alter the

interaction between the body's immune system and the tumor cells by inducing, boosting, or restoring the body's defense ability to fight cancer. Several BRMs have been shown to be effective as a standard part of treatment for certain types of cancer. They are also being used in conjunction with other treatments, such as radiation therapy and chemotherapy. Researchers still continue to discover new BRMs, and to develop ways to use them in cancer therapy.

Conflict of Interests

The Authors declare no conflict of interests.

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