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RECENT ADVANCES IN CANCER IMMUNOTHERAPY: A REVIEW

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SUMMARY
Immunotherapy is the treatment of disease by activating or suppressing the immune system. Immunotherapies designed to elicit or amplify an immune response are classified as activation immunotherapies while immunotherapies that reduce or suppress the immune system are classified as suppression immunotherapies. The objective of this review is to examine recent advances in cancer immunotherapy. Previous works and research findings on this subject were accessed through Google Search, PubMed, and Wikipedia websites. In addition, standard textbooks on Pharmacology were consulted. All these sources provided necessary information for this review on recent advances in cancer immunotherapy. Types of immunotherapy that are used in cancer treatment include the following: monoclonal antibodies, oncolytic virus therapy, non-specific immunotherapies, T cell transfer therapy, cancer vaccines, and dendritic cell-based pump-priming. There are several side effects associated with immunotherapy. These include skin changes, flu-like symptoms, palpitations, diarrhea, sinus congestion, and allergic reactions. Recent advances involve the use of checkpoint inhibitors (CPIs) such as ipilimumab, nivolumab, pembrolizumab, atezolizumab, avelumab, and durvalumab. Current trends in immunotherapy involve combination therapy with CPIs such as combination of CPIs and cancer chemotherapy, combination with radiotherapy, combination with immunomodulatory drugs.

KEYWORDS: Immunotherapy, CPIs, immune response, cancer chemotherapy.

INTRODUCTION

Immunotherapy is a type of cancer treatment that boosts the body's immune system and helps it to fight cancer. It uses materials made by the body or in a laboratory to target and enhance a person's immune system. Immunotherapy is a type of biological therapy. Biological therapy is a type of treatment that uses substances made from living organisms to treat cancer.[1]

Immunotherapy is not just about the treatment of cancer alone, although it gained prominence in recent years because of the prospect of using it to treat various forms of cancer.[2,3] Broadly speaking, immunotherapy is treatment of disease by activating or suppressing the immune system. Immunotherapies designed to elicit or amplify an immune response are classified as activation immunotherapies while immunotherapies that reduce or suppress the immune system are classified as suppression immunotherapies.

Justification for the use of immunotherapy is based on the fact that immunomodulatory regimens often have fewer side effects than the existing drugs. Secondly, they have less potential for creating resistance when treating microbial disease.[4]

Furthermore, cell-based immunotherapies are effective for some cancers. Immune effector cells such as lymphocytes, macrophages, dendritic cells, natural killer cells (NK cells), cytotoxic T lymphocytes (CTL) work together to defend the body against cancer by targeting abnormal antigens expressed on the surface of tumor cells. The immune system helps the body to resist almost all types of organisms or toxins that tend to damage the

tissues and organs. There are different types of immunity:

Innate Immunity

Innate immunity is the inborn capacity of the body to resist pathogens. If organisms enter the body accidentally, innate immunity eliminates them before the development of any disease. It results from general processes rather than processes directed at specific disease organisms. It includes the following:

- Phagocytosis of bacteria and other invaders by white blood cells and cells of the tissue macrophage system.
- Destruction of swallowed organisms by the acid secretions of the stomach and the digestive enzymes.
- Resistance of the skin to invasion by organisms.
- Presence in the blood of certain chemical compounds that attach to foreign organisms or toxins and destroy them. Some of these compounds are: (i) Lysozyme, a mucolytic polysaccharide that attacks bacteria and cause them to dissolute. (ii) Basic polysaccharides which react with and inactivate certain types of gram-positive bacteria. (iii) The complement complex.(iv) Natural killer lymphocytes that recognize and destroy foreign cells, tumor cells, and even some infected cells.[5]

Acquired immunity

Acquired immunity is the resistance developed in the body against any specific foreign body like bacteria, viruses, toxins, vaccines, or transplanted tissues. This type of immunity is also called specific or adaptive immunity. Acquired immunity is caused by a special immune system that forms antibodies and/or activated lymphocytes that attack and destroy the specific invading organism or toxin. There are two types of acquired immunity: (i) Humoral immunity or B-cell immunity: B-lymphocytes produce antibodies called globulin molecules that are capable of attacking the invading agent. The antibodies are gammaglobulins called immunoglobulins (Ig). They are composed of combinations of light and heavy polypeptide chains. Most are a combination of two light and two heavy chains. There are five general classes of antibodies: IgM, IgG, IgA, IgD, and IgE. IgG is a bivalent antibody that constitutes about 75% of the antibodies of normal person. IgE constitutes only a small percentage of the antibodies and is especially involved in allergy. (ii) Cell-mediated immunity or T cell immunity. There is formation of large numbers of activated T-lymphocytes that are specifically crafted in the lymph nodes to destroy the foreign agent.[6]

Types of T cells

(a) Helper T cells. They are by far the most numerous of the T cells, usually constituting more than three quarters of all of them. They help in the functions of the immune system. They do this by forming a series of protein mediators, called lymphokines that act on other cells of the immune system as well as on bone marrow cells. Among the important lymphokines secreted by the helper T cells are the following: Interleukin-2, Interleukin-3, Interleukin-4, Interleukin-5, Interleukin-6, Granulocyte monocyte colony stimulating factor, Interferon- gamma.
In the absence of the lymphokines from the helper T cells the remainder of the immune system is almost paralyzed. In fact, it is the helper T cells that are inactivated or destroyed by HIV, which leaves the body almost totally unprotected against infectious disease.[5]

(b) Cytotoxic T cells. The cytotoxic T cells are direct attack cells that are capable of killing own cells. For this reason these cells are called killer cells.

(c) Suppressor T cells. They are capable of suppressing the function of both cytotoxic and helper T cells. It is believed that these suppressor functions serve the purpose of preventing the cytotoxic cells from causing excessive immune reactions that might be damaging to the body's own tissues.[7]

Both types of acquired immunity are initiated by antigens. Each toxin or each type of organism almost always contains one or more specific chemical compounds in its make-up that are different from all other compounds. In general, these are proteins or large polysaccharides and it is they that initiate the acquired immunity. These substances are called antigens.

Acquired immunity is product of the body's lymphocytes. In people who have a genetic lack of lymphocytes or whose lymphocytes have been destroyed by radiation or chemicals, no acquired immunity can develop. And within days after birth, such a person dies of fulminating bacterial infection unless urgent treatment is given.[6]

Cells of the immune system

- **Monocytes.** Monocytes enter the blood from the bone marrow and circulate for about 72 hours. They then enter the tissues and become tissue macrophages. Their life span in the tissues is unknown but bone marrow transplantation data in humans suggest that they persist for about three months. It appears that they do not reenter the circulation. Some of them end up as the multinucleated giant cells in the chronic inflammatory disease such as tuberculosis. The tissue macrophages include the kupffer cells of the liver, pulmonary alveolar macrophages, osteoclasts, and all come from the circulation. The macrophages become activated by lymphokines from T-lymphocytes. The activated macrophages migrate in response to chemotactic stimuli and engulf and kill bacteria.[6]
- **Natural killer cells.** A third type of lymphocyte found in the body is the natural killer cell (NK cell), which is sometimes called the non T, non-B lymphocyte. The natural killer cells are large lymphocytes that make up 10-15% of the

circulating mononuclear cells. They kill cells without any apparent prior sensitization and without the involvement of major histocompatibility antigens. They destroy cells that have undergone malignant transformation and so help prevent the establishment of tumors. In addition, they attack viruses and Fc receptors that permit them to kill antibody coated viruses. Their activity is increased by IL-2. Current evidence indicates that they represent an important first line of defense against viral infections, combating the spread of disease while the more specific T and B cell responses are activated. In addition, they may represent a primitive immune system from which the T and B cell system evolved.[5]

Immune tolerance

The body naturally does not launch an immune system attack on its own tissues. Immune tolerance therapies seek to reset the immune system so that the body stops mistakenly attacking its own organs or cells in autoimmune disease or accepts foreign tissue in organ transplantation. Creating immunity reduces or eliminates the need for lifelong immunosuppression and attendant side effects. It has been tested on transplantation and other autoimmune disorders.[8]

Allergies

Immunotherapy is used to treat allergies. While conventional drugs are used to treat allergy (e.g. antihistamine or corticosteroids) immunotherapy can reduce sensitivity to allergens, thereby decreasing its severity.[9]

Immunotherapy offers allergy sufferers a chance to reduce or stop their symptoms. It is partly effective in some people and ineffective in others. Immunotherapy has been shown to produce long-term benefits. Immunotherapy involves giving gradually increasing doses of the substance or allergen to which the person is allergic. The incremental increases of the allergen cause the immune system to become less sensitive to substance, probably by causing production of 'blocking' antibody, which reduces the symptoms of allergy when the substance is encountered in the future.[10] Drugs used in immunotherapy to treat asthma are:

(a) Reslizumab (Cinqair) is an immunomodulator maintenance medication. It is used along with regular asthma medicines. This drug works by reducing the number of eosinophils in the body. It is given intravenously.
(b) Mepolizumab (Nucala) targets the level of blood eosinophils. It is given as an injection every 4 weeks and is used as a maintenance therapy medication.
(c) Omalizumab (Xolair) is an antibody that blocks immunoglobulin E (IgE) and is used as an asthma maintenance medication. This drug is given as an injection.[11]

The therapy is indicated for people who are extremely allergic or who cannot avoid specific allergens. It is particularly useful for people with allergic rhinitis or asthma. Immunotherapy is generally not indicated for food or medicinal allergies. The first dose contains tiny amounts of the allergen or antigen. Doses increase over time as the person becomes desensitized. This technique has been tested on infants to prevent peanut allergies.[9]

Immunomodulators

Immunomodulators are the active agents of immunotherapy. They are either immunostimulants or immunosuppressants. They encompass an array of recombinant, synthetic, and natural preparations.

The classes are

- Interleukins: IL-2, IL-7, IL-12
- Cytokines: interferons, G-CSF (granulocyte colony-stimulating factor)
- Chemokines: CCL3, CCL26, CXCL7
- Immunomodulatory imide drugs (IMiDs): thalidomide and its analogues (Lenalidomide, pomalidomide, and apremilast).[12]

Types of immunotherapies in the treatment of cancer

1) Monoclonal antibodies and tumor-agnostic therapies

Monoclonal antibodies are antibodies that arise from a single clone of cells (e.g., myeloma). They are homogenous and are called monoclonal antibodies. For example, in multiple myeloma, antibodies are produced by a single clone of plasma cells against a single antigenic determinant, and hence antibodies are monoclonal. The monoclonal antibodies differ from polyclonal antibodies, which are heterologous and are formed by several different clones of plasma cells in response to antigen. Kohler and Milstein were the first to describe a method for production of monoclonal antibodies against a desired antigen for which they were awarded Nobel Prize in 1984. Monoclonal antibodies are produced by fusion of myeloma cells with antibody-producing cells, resulting in production of hybridomas. Such hybridomas produce virtually unlimited quantities of antibodies that are useful in research and diagnostics. In this procedure, mouse splenic lymphocytes are first fused with mouse myeloma cells to produce hybrid cells or hybridomas. Myeloma cell provides the hybrid cell immortality, whereas splenic plasma cell provides the antibody- producing capacity. These hybridomas can be maintained indefinitely in culture and continue to produce monoclonal antibodies.[13] Hybridoma cells are prepared in following ways:

- First, an animal (e.g., mouse) is immunized with the antigen of interest.
- Spleen cells (lymphocytes) are then fused with mouse myeloma cells and grown in culture, which are deficient in the enzyme hypoxanthine phosphoribosyl transferase (HPRT).
- Fusion of the cells is facilitated by addition of certain chemicals, such as polyethylene glycol. The fused cells are grown in a special culture medium

(HAT medium) that supports the growth of the fused hybrid cells but not of the parent cells.
- Finally, the resulting clones of cells are screened for the production of antibody to the antigen of interest.
- These clones are then selected for continuous cultivation. The hybridomas can be maintained indefinitely and will continue to produce monoclonal antibodies.[14]

Polyclonal antibodies, on the other hand, are made using several different immune cells. They have affinity for the same antigen but different epitopes. Polyclonal antibodies are produced by injecting an immunogen into an animal. After being injected with a specific antigen to elicit a primary immune response the animal is given a secondary even tertiary immunization to produce higher titers of antibodies against the particular antigen. After immunization, polyclonal antibodies can be obtained straight from the serum or purified to obtain a solution which is free from other serum proteins.[15]

Monoclonal antibodies are a specific type of therapy made in a laboratory. They may be used in a variety of ways. For example, monoclonal antibodies can be used as a targeted therapy to block an abnormal protein in a cancer cell. Monoclonal antibodies can also be used as an immunotherapy. For example, some monoclonal antibodies attach to specific proteins on cancer cells. This activates the immune system to find and destroy those cells perceived as foreign body.[16]

Other monoclonal antibodies attach to and inactivate growth factors or their receptors on cancer cells, thus inhibiting their survival pathway and promoting apoptosis.[16]

Monoclonal antibodies can be classified into first –or second-generation reagents. First-generation monoclonal antibodies were essentially murine monoclonal antibodies, but these suffered from several drawbacks. As mouse proteins, they provoked an immune response in 50-75% of all recipients. Other limiting factors were a short half-life in the circulation and the inability of the mouse antibodies to activate human complement. Most of these problems have been surmounted by using either chimeric or humanized monoclonal antibodies.[17]

Humanization of murine antibody

Antibody humanization methods are designed to produce a molecule with minimal immunogenicity when applied to humans, while retaining the specificity and affinity of the parent non-human antibody. Humanization began with chimerization, a method developed during the first half of the 1980's. Chimeric antibodies successfully retained the mouse parent antibody specificity and diminished its immunogenicity but still elicited a human anti-chimeric antibody (HACA) response.[18]

There are two trends in the field of humanization: rational and empirical methods.

(1) Rational methods. Rely on the so-called design cycle. It consists of generating a small set of variants, which are designed based on the antibody structure and/or sequence information, and assessing their binding or any other characteristic of interest. Rational methods include: CDR (complimentarity-determining region) grafting, Resurfacing, Superhumanization and Human String Content Optimization.[19]
(2) Empirical methods are based on generating large combinatorial libraries and selecting the desired variants by enrichment technologies such as phage, ribosome or yeast display, or by high throughput screening techniques.[19]

Examples of monoclonal antibodies

(a) Rituximab

Rituximab is a monoclonal antibody that is used (in combination with other chemotherapeutic agents) for the treatment of certain types of lymphoma. It lyses B lymphocytes by binding to calcium channel forming CD20 protein and activating complement. It also sensitizes resistant cells to other chemotherapeutic drugs. It is effective in 40-50% of cases when combined with standard chemotherapy. The drug is given by infusion, and its plasma half-life is approximately 3 days when first given, increasing with each administration to about 8 days by the fourth administration. Unwanted effects are hypotension, chills and fever during the initial infusions and subsequent hypersensitivity reactions. A cytokine release reaction can occur and has been fatal. The drug may exacerbate cardiovascular disorders.[13]

(b) Trastuzumab

Trastuzumab is a humanized murine monoclonal antibody that binds to an oncogenic protein termed HER2 (the human epidermal growth factor receptor-2), a member of the wider family of receptors with integral tyrosine kinase activity. In addition to inducing host immune responses, trastuzumab induces cell cycle inhibitors p21 and p27. Tumor cells, in about 25% of breast cancer patients, overexpress this receptor and the cancer proliferates rapidly. Trastuzumab given with standard chemotherapy has resulted in a 79% 1-year survival rate in treatment-naïve patients with this aggressive form of breast cancer. The drug is often given with a taxane such as docetaxel. Unwanted effects are similar to those with rituximab.[13]

(c) Bevacizumab

It is a humanized monoclonal antibody that is used for the treatment of colorectal cancer. It neutralizes VEGF (vascular endothelial growth factor), thereby preventing the angiogenesis that is crucial to tumor survival. It is administered by intravenous infusion and is generally combined with other agents.

(d) Catumaxamab

Catumaxamab attaches to an epithelial adhesion molecule, EpCAM, which is overexpressed in some

malignant cells (e.g. malignant ascites in the peritoneal cavity). The antibody binds to this adhesion molecule and also to T lymphocytes and antigen-presenting cells, thus facilitating the action of the immune system in clearing the cancer.

(2) Oncolytic virus therapy. Oncolytic virus therapy uses genetically modified viruses to kill cancer cells. First, the virus is injected into a tumor. The virus then enters the cancer cells and makes copies of it. As a result, the cells burst and die. As the cells die, they release specific substances called antigen. This triggers the patient's immune system to target all the cancer cells in the body that have these same antigens. The virus does not enter healthy cells. In 2015, the US Food and Drug Administration (FDA) approved the first onclytic virus therapy to treat melanoma. The virus used in the treatment was called talimogene laherpareprec (Imlygic) or T-VEC. The virus is a genetically modified version of the herpes simplex virus that causes cold sores.[16] Researchers are testing other oncolytic viruses for different types of cancer in clinical trials. Injection immunotherapy (intralesional or intratumoral) uses mumps, the human papilloma virus (HPV) to treat warts (HPV induced tumors).[20]

(3) Non-specific immunotherapies. Like monoclonal antibodies, non-specific immunotherapies also help the immune system destroy cancer cells. Some non-specific immunotherapies are given in combination with chemotherapy or radiotherapy. Others are given as the main cancer treatment.

(i) Interferons. Interferons (IFNs) are the glycoprotein molecules that are produced by white blood cells (WBC), NK cells, fibroblasts. They are considered as antiviral agents. There are three types of interferons: interferon-alpha, interferon-beta, and interferon-gamma. Interferons help the immune system fight cancer and may slow the growth of cancer cells. The actions of interferons include: fighting against viral infection by suppressing virus multiplication in target cells; inhibition of multiplication of parasites and cancer cells; promotion of phagocytosis by monocytes and macrophages; activation of NK cells. A type of interferon made in a laboratory is called interferon alpha. Interferon stimulates NK cell function.[14]

(ii) Interleukins. Interleukins (IL) are the polypeptide cytokines which are produced mainly by the leukocytes and act on other leukocytes. They help the immune system produce cells that destroy cancer. Interleukins carry out their actions by the following methods: activation of T cells, macrophages, and natural killer (NK) cells; promotion of hematopoietic cells and B cells; acceleration of inflammatory response by activating eosinophils; chemotaxis of neutrophils, eosinophils, basophils, and T cells; destruction of invading organisms. An interleukin made in a laboratory is called interleukin-2, IL-2 or aldesleukin (proleukin). Cytokine IL-2 stimulates the killing of cancer cells by cytotoxic T cells. It is used to treat kidney cancer and skin cancer, including melanoma. Common side effects of IL-2 treatment include weight gain and low blood pressure.[16]

(iii) Corynebacterium parvium is an anaerobic diptheroid organism that possesses antitumor activities. Its antitumor effect is due to its ability to stimulate macrophages and B cells. It shows a synergistic effect when used in conjunction with cyclosphamide. It is found to be useful in treatment of metastatic breast cancer and various types of lung cancer.[14]

(iv) Levamisole is a medication used to treat parasitic worm infestations. It is used for ascariasis and hookworm infestation. Levamisole has been tested in combination with fluorouracil to treat colon cancer. Dinitrochlorobenzene (DNCB) is an organic compound. It is an important intermediate for the industrial production of other compounds. DNCB can be used to treat warts with an effective cure rate of 80%. It has been evaluated in squamous and basal carcinoma.[16] (vi) Bacillus Calmette Guerin (BCG) vaccine has been shown to possess antitumor activity. The vaccine when injected directly into certain solid tumors may cause regression of tumor. Its antitumor effect is due to activation of macrophages and NK cells. The BCG therapy has been reported to be beneficial in treatment of malignant melanoma, stage 1 lung cancer, and bladder cancer.[14,21]

(4) T-cell transfer therapy. T cells are immune cells that fight infection. In T cell therapy some T cells are removed from a patient's blood. The cells are changed in a laboratory so that they have specific proteins called receptors. The receptors allow those T cells to recognize the cancer cells. The changed T cells are grown in the laboratory and returned to the patient's body. Once there, they seek out and destroy cancer cells. This type of therapy is called chimeric antigen receptor (CAR) T-cell therapy. The technique has been tested on refractory stage IV metastatic melanomas and advanced skin cancer.[22]

Before reinfusion lymphodepletion of the recipient is required to eliminate regulatory T cells as well as unmodified endogenous lymphocytes that compete with the transferred cells for homeostatic cytokines.[23,24]

Lymphodepletion may be achieved by myeloablative chemotherapy to which total body irradiation may be added for greater effect. Clinical responses to adoptive transfer of T cells were observed in patients with metastatic melanoma resistant to multiple immunotherapies.[25]

Tumor infiltrating lymphocytes (TILs) are white blood cells that have moved from the blood into a tumor to try and attack the cancer. They are lymphoid cells that infiltrate solid tumors and appear naturally reactive to autologous tumor antigens. They directly oppose and surround tumor cells. The presence of intratumor TILs is an important piece of evidence for immune response between tumor cells and immune effector cells. It has been shown that the presence of lymphocytes in tumors is often associated with better clinical outcomes after

surgery or immunotherapy.[3]

(5) Cancer vaccines. A cancer vaccine is another method used to help the body fight disease. A vaccine exposes the immune system to an antigen. This triggers the immune system to recognize and destroy that antigen or related materials. There are two types of cancer vaccines: preventive vaccines and treatment vaccines.[16] Some types of cancer, such as cervical cancer and some liver cancers are caused by viruses (oncoviruses). Traditional vaccines against those viruses, such as the HPV vaccine and hepatitis B vaccine, prevent those types of cancer. Other cancers are to some extent caused by bacterial infections (e.g. stomach cancer and helicobacter pylori).[16]

There are two types of vaccines that prevent cancer approved by the US Food and Drug Administration (FDA): (1) HPV Vaccine. The vaccine protects against the human papillomavirus (HPV). The FDA has approved HPV to prevent: (a) cervical, vaginal, and vulvar cancers. (b) Anal cancer. (c) Genital warts. HPV can also cause other cancers the FDA has not approved the vaccine for, such as oral cancer. (2) Hepatitis B Vaccine. This vaccine protects against the hepatitis B virus (HBV). This virus can cause liver cancer.[16]

A therapeutic vaccine is a vaccine which is administered after the disease or infection has already occurred. The therapeutic vaccine works by activating immune system of the patient to fight towards infection. The difference in therapeutic vaccine and vaccine is that vaccines are administered to individuals as a precautionary measure to avoid the infection or disease while therapeutic vaccines are administered after the individual is already affected by the disease or infection. Therapeutic vaccine fights the existing infection in body rather than immunizing body for protection against future diseases and infections. Patients affected with chronic viral infections are administered with therapeutic vaccines, as their immune system is not able to produce enough efficient antibodies. Provenge was the first therapeutic vaccine approved by FDA in 2010, which was developed by Dendreon. This therapeutic vaccine helped in treating prostate cancer.[26,27] Dendritic cell-based pump-priming: dendritic cells can be stimulated to activate a cytotoxic response towards an antigen. Dendritic cells, a type of antigen presenting cell, are harvested from the person needing the immunotherapy. These cells are then either pulsed with an antigen or tumor lysate or transfected with a viral vector, causing them to display the antigen. Upon transfusion into the person, these activated cells present the antigen to the effector lymphocytes (CD4+ helper T cells, cytotoxic CD8+ T cells and B cells). This initiates a cytotoxic response against tumor cells expressing the antigen (against which the adaptive response has been primed). The cancer vaccine Sipuleucel-T is one example of this approach.[27,28]

Routes of administration of immunotherapy

They include intravenous, oral, topical, intravesical (into the bladder)

Side effects of immunotherapy

(1) Skin changes: Pain, swelling, soreness, redness, itchiness, rash.
(2) Flu-like symptoms: fever, chills, weakness, dizziness, nausea or vomiting, muscle or joint aches, fatigue, headache, difficulty in breathing.
(3) Others: Swelling and weight gain, palpitations, diarrhea, sinus congestion, allergic reactions.[1]

Some cancers that have responded to immunotherapy

Some cancers have responded to immunotherapy, especially at early stages. They include:

- Bladder, brain, breast, cervical, childhood, colorectal, esophageal cancers
- Head and neck, kidney, liver, lung, ovarian, pancreatic, prostate cancers
- Leukemia, lymphoma, melanoma, multiple myeloma
- Stomach and uterine cancers.[29]

Recent advances in cancer immunotherapy

The field of immunotherapy is expanding. Researchers are discovering novel approaches to make immunotherapy relevant in modern cancer treatment. In 2018, two scientists P Allison and Tasuku Horijo were awarded Nobel prize in Physiology or Medicine for the discovery of cytotoxic T lymphocyte associated protein (CTL A) and programmed cell death protein 1/ programmed cell death protein ligand 1 (PD-1/PD-L1) respectively. PD-1/PD-L1 and CTL A -4 pathways are critical to the immune system's ability to control cancer growth. These pathways are often called immune checkpoints. Malignant tumors take advantage of these pathways to evade the immune system. Disruption of this immune checkpoints by blocking monoclonal antibodies can induce durable remissions in different cancer types and has led to numerous FDA approvals for the treatment of melanoma, lung cancer, urothelial cancer, head and neck squamous cell carcinoma (HNSCC), renal cell cancer (RCC).[30]

Immune checkpoint inhibitors

Immune checkpoint inhibitors are drugs that block certain proteins made by some types of immune system cells such as T cells and some cancer cells. These proteins help keep immune responses in check and can keep T cells from cancer cells. When these proteins are blocked, the inhibition on the immune system is released and T cells are able to kill cancer cells better. Examples of checkpoint proteins found on T cells or cancer cells include PD-1/PD-L1 and CTLA-4/B7-1/B7-2.

Checkpoint proteins such as PD-L1 on tumor cells and PD-1 on T cells help keep immune response in check. The binding of PD-L1 to PD-1 keeps T cells from killing tumor cells in the body. Blocking the binding of PD-L1

to PD-1 with an immune checkpoint (anti-PD-L1 or anti-PD-1) allows the T cells to kill tumor cells.

Checkpoint proteins such as B7-1/B7-2 on antigen-presenting cells (APC) and CTLA-4 on T cells help keep the body's immune response in check. When the T cell receptor (TCR) binds to antigen and major histocompatibility complex (MHC) proteins on the APC and CD28 binds to B7-1/B7-2 on the APC the T cell can be activated. However, the binding of B7-1/B7-2 to CTLA-4 keeps the T cells in the inactive state so they are not able to kill tumor cells in the body. Blocking the binding of B7-1/B7-2 to CTLA-4 with an immune checkpoint inhibitor (anti-CTLA-4 antibody) allows the T cells to be active and kill tumor cells.[1]

The following are examples of immune checkpoint inhibitors

- Ipilimumab (Yervoy). Ipilimumab is a monoclonal antibody that attaches to CTLA-4 and stops it from working. This can boost the body's immune response against cancer cells. This drug is used to treat melanoma of the skin. It has more serious side effects than other CPIs.[12]
- Nivolumab (Opdivo). Nivolumab is an antibody that binds to PD-1, blocks interaction of PD-L1 (ligand) withPD-1, with consequent blocking of the PD-L1/PD-1 signalling pathway. It received FDA approval in 2015 for the treatment of non-small cell lung cancer (NSCLC).[31]
- Pembrolizumab (Keytrida). Pembrolizumab is an FDA approved monoclonal antibody sold in the US. Its mechanism of action is blockade of programmed cell death protein 1 (PD-1) pathway. It was approved for the treatment of refractory advanced melanoma in 2014.[32]
- Atezolizumab (Tecentriq)
- Avelumab (Bavencio)
- Durvalumab (Imfinzi).[33]

Current trends in cancer immunotherapy

Current trends focus on various ways checkpoint inhibitors are being used in cancer immunotherapy.

- **Checkpoint inhibitors.** Some researchers showed that antineoplastic effect of chemotherapy in part, depended on the immunogenic cell death of cancer cells. Before then it was thought that chemotherapy and radiotherapy killed cancer cells directly.[34] This lead to the development of combinational regimens using PD-1/PD-L1 blockade together with established chemotherapeutic drugs.[35,36] A lot of work is going on along this direction. At present more than 170 studies are investigating the promising combination of PD-1/PD-L1 blockade plus chemotherapy in different cancer entities.[37]
- **Combination with radiotherapy.** It has been reported that there is a clear relationship between local radiation, immunogenic cell death and systemic tumor response. Numerous strategies are being investigated to harness the immunogenic effect of radiotherapy. Pre-clinical evidence highlights the synergistic potential of this combination.[38,39] It is important to note that combination of checkpoint inhibitors and radiotherapy is not success story all the way. Negative result has equally been reported.[40]
- **Combination with immunomodulatory drugs.** The first CPI approved for clinical use was ipilimumab, targeting CTL A-4. Given the success of ipilimumab and greater success of PD-1 blockade. It is not surprising that out of more than 250 clinical trials, the combination of PD-1 and CTL A-4 blockade is the most vigorously investigated combinational approach of two immunomodulatory drugs.[37] Careful selection is required because some combinations may be antagonistic instead of synergistic.
- **Peri-operative use.** Peri-operative use of CPIs appears promising at least from theoretical perspective. Research result showed that the efficacy of CPIs depended on baseline tumor burden, with better efficacy observed in patients with low tumor burden. Therefore, using CPIs peri-operatively may be a good treatment option.[41]

CELLULAR IMMUNOTHERAPY

Chimeric antigen receptor T cells

Tisagenlecleucel (marketed as **Kymriah**) and *axicabtagen-ciloleucel* (marketed as **Yescarta**) were the first two cellular cancer immunotherapies that received FDA approval in 2017 and 2018 respectively. They are approved to treat patients with acute lymphoblastic leukemia (ALL, *tisagenlecleucel*) and diffuse large B cell lymphoma (DLBCL, *tisagenlecleucel* and *axicalbtagen-ciloleucel*). These two cellular cancer immunotherapies are autologous T cell products. After leukapheresis, T cells are genetically engineered to express an anti-CD19 chimeric antigen receptor (anti-CD19 CAR T cells). Re-infusion of CAR T cells is preceded by a lympho-depleting chemotherapy to allow for subsequent in vivo expression of CAR T cells.[42]

CONCLUSION

Immunotherapy focuses primarily on cancer treatment, although there are other aspects like allergy immunotherapy. Substances that are produced by living organisms are used to treat disease by boosting the immune system. The field of immunotherapy is expanding. Researchers are discovering novel approaches to make immunotherapy relevant in modern cancer treatment.

REFERENCES

1. National Cancer Institute (NCI) (2019). Immunotherapy to treat cancer. Available online, https://www.cancer.org/about-cancer/treatment/types/immunotherapy.
2. Conforti L, The ion channel network in T lymphocytes, a target for immunotherapy. Clin Immunol, 2012; 142(2): 105-106.

3. Syn NL, Teng MW, Mok TS, Soo RA, De novo and acquired resistance to immune checkpoint targeting. The Lancet. Oncology, 2017; 18(12): e731-e741.
4. Masihi KN, Fighting infection using immunomodulatory agents. Expert Opin Biol Ther., 2001; 1(4): 641-53.
5. Sembulingam K and Sembulingam P, Immunity. Essentials of medical physiology. 7th edition. New Delhi. Health Sciences Publishers, 2016.
6. Guyton AC and Hall JE, Textbook of medical physiology. 12th edition. Philadelphia, Elsevier, 2011.
7. Waugh A and Grant A, Resistance and immunity. Ross & Wilson Anatomy and Physiology in health and illness. 13th edition. Edinbuurgh, Elsevier, 2018.
8. Rotrosen D, Matthews JB, Bluestone JA, The immune tolerance network: a new paradigm for developing tolerance-inducing therapies. The Journal of Allergy and Clincal Immunology, 2002; 110(1): 17-23.
9. Stanford University School of Medicine (SUSM) (2016). Clinical trials search results. Available online, https: //www.med.stanford.edu.
10. American College of allergy, asthma & immunology (ACAAI) (2021). Allergy immunotherapy. Available online, https://acaai.org (Accessed: February, 2021).
11. WebMD, (2020). Asthma medications. Available online, https://www.webmd.com.
12. American Cancer Society (ACS) (2021). Immunomodulators and their side effects. Available online, https://www.cancer.org.(Accessed: February, 2021).
13. Rang HP, Ritter JM, Flower RJ, Henderson G. Anticancer drugs. Rang and Dale's Pharmacology. 8th edition.Elsevier, Churchill-Livingstone, 2016; 687-9.
14. Parija SC. Textbook of Microbiology and Immunology.Second edition. Elsevier, India, 2012.
15. Labclinics, (2018). Monoclonal and polyclonal antibodies, https://www.labclinics.com.
16. Cancer. Net (2019). Understanding immunotherapy. Available online, https://www.cancer.net.
17. Walsh G, Second-generation biopharmaceuticals. Eur J Pharm Biopharm, 2004; 58: 185-196.
18. Hwang WY and Foote J, Immunogenicity of engineered antibodies. Methods, 2005; 36: 3-10.
19. Almagro JC and Franson J. Humanization of antibodies. Frontiers in Bioscience, 2008; 13: 1619-1633.
20. Chuang CM, Monie A, Wu A, Hung CF, Combination of apigenin treatment with therapeutic HPV DNA vaccination generates enhanced therapeutic antitumor effects. J Biomed Sci., 2009; 16(1): 49.
21. Fuge O, Vasdev N, Allchorne P, Green JS, Immunotherapy for bladder cancer. Research and Reports in Urology, 2015; 7: 65-79.
22. Highfield R, (2008). Cancer patient recovers after injection of immune cells. The Telegraph. Retrieved 22 December, 2019.
23. Dummer W, Niethammer AG, Baccala R, Lawson BR, Wagner N, Reisfeld RA, Theofilopoulos AN, T cell homeostatic proliferation elicits effective antitumor autoimmunity. J Clin Invest, 2002; 110(2): 185-92.
24. Gattinoni L, Finkelstein SE, Klebanoff CA, Antony PA, Palmer DC, Spiess PJ, Hwang LN, Yu Z, Wrzesiniski C, Heimann DM, Surh CD, Rosenberg SA, Restifo NP, Removal of homeostatic cytokine sinks by lymphodepletion enhances the efficacy of adoptively transferred tumor-specific CD8+ Tcells. J Exp Med., 2005; 202(7): 907-12.
25. Andersen R, Borch TH, Draghi A, Gokuldass A, Rana MA, Pedersen M, T. cells isolated from patients with checkpoint inhibitor resistant-melanoma are functional and can mediate tumor regression. Ann Oncol, 2018; 29(7): 1575-1581.
26. Gulley J. Therapeutic vaccines, the ultimate personalized therapy. Human vaccine & immunotherapeutics, **2012; 9**(1): 219-221.
27. Food and Drug Administration of the US (FDA) (2021). Provenge (Sipuleucel-T). Available online, https://www.fda.gov. (Accessed: January, 2021).
28. Di Lorenzo G, Buonerba C, Kantoff PW, Immunotherapy for the treatment of prostate cancer. Nature Reviews Clinical Oncology, 2011; 8(9): 551-61.
29. Cancer Research Institute (2020). Immunotherapy for all cancer types. Available at: www.cancerresearch.org.
30. Gong J, Chehrazi-Raffle A, Raddi S, Salgia R, Development of PD-1 and PD-L1 inhibitors as a form of cancer immunotherapy: a comprehensive review of registration, trials and future considerations. J Immunother Cancer, 2018; 6(1): 8.
31. Tanoue L, Detterbeck F, (2018). Lung cancer: a practical approach to evidence-based clinical evaluation and management. Available online, https://doi.org/10.1016/c2016-0-01357-8.
32. Flynn JP, Gerriets V, (2019).Pembrolizumab. In: StatPlearls[internet]. Treasure Island (FL). StartPearls Publishing, https://www.ncbi.nim.nih.gov.
33. Bansal P, Osman D, Gan GN, Simon GR, Boumber Y, Recent advances in immunotherapy in metastatic NSCLC. Front Oncol, 2016; 6: 239.
34. Apetoh I, Ghiringhelli F, Tesniere A, Oheid M, Oritiz C, Criollo A, Toll-like receptor 4-dependent contribution of the immune system to anticancer chemotherapy and radiotherapy Nar Med., 2007; 13(9): 1050-9.
35. Hato SV, Khong A, de Viries IJ, Lesterhuis WJ, Molecular pathways: the immunogenic effects of platinum-based chemotherapeutics. Clin Cancer Res., 2014; 20(11): 2831-7.
36. Gulluzi I, Guque A, Kepp O, Zitvagel I, Kroemer G, Immunological effects of conventional chemotherapy and targeted anticancer agents. Cancer Cell., 2015; 28(6): 690-714.

37. Tang I, Shalabi A, Hubbard-Lucey VM, Comprehensive analysis of the clinical immune-oncology landscape. Ann Oncol, 2018; 29(1): 84-91.
38. Park SS, Dong H, Liu X, Harrington SM, Kico CJ, Grams MP, PD-1 restrains radiotherapy-induced abscopal effect. Cancer Immunol Res., 2015; 3(6): 610-9.
39. Manukian G, Bar-Ad V, Lu B, Argiris A, Johnson JM (2019). Combining radiation and immune checkpoint blockade in the treatment of head and neck squamous cell carcinoma. Front Oncol 06 March, 2021, https://doi.org/10.3389/fonc.201900122.
40. McBride SM, Sherrian EJ, Tsai CJ, Baxi SS, Aghalar J, Eng J, A phase II randomized trial of nivolumab with stereotactic body radiotherapy (SBRT) versus nivolumab alone in metastatic (M1) head and neck squamous cell carcinoma (HNSCC). J Clin Oncol, 2018; 36(15): 6009.
41. Joseph RW, Elassaiss-Schaap J, Kefford R, Hwu WJ, Wolchok JD, Joshua AM, Baseline tumor size is an independent prognostic factor for overall survival in patients with melanoma treated with pembrolizumab. Clin Cancer Res., 2018; 24(20): 4960-7.
42. Kruger S, Ilmer M, Kobold S, Cadilha BL, Endres S, Advances in cancer immunotherapy 2019 ─ latest trends. J Exper & Clin Cancer Res., 2019; 38: 268.