TIU Transactions on Human sciences

Immunomodulation in cancer

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Abstract

A potentially effective method of treating cancer is immunomodulation, which uses the immune system's capacity to identify and eradicate tumor cells. This abstract highlights the possibility for individualized and successful treatment by summarizing the state of the art and recent developments in immunomodulation methods for cancer. Immunotherapies target immune evasion strategies used by cancer cells and improve anti-tumor immune responses by modifying T-cells, natural killer cells, and antigen-presenting cells, among other immune system components. Immune checkpoint inhibitors, cancer vaccines, chimeric antigen receptor (CAR) T-cell treatment, and adoptive cell transfer are some of the important immunomodulatory strategies that were covered. These treatments have shown impressive clinical results, with long-lasting responses and higher survival rates shown in a range of cancers, such as melanoma, lung cancer, and hematological malignancies.

1. Introduction

Immunomodulation has become a cutting-edge method of treating cancer that gives patients fresh hope and opportunities. The immune system is essential for identifying aberrant cells, such as cancer cells, and getting rid of them. But cells, even those that are cancerous. On the other hand, cancer cells have evolved a number of evasion tactics to avoid immune recognition and elimination. The goal of immunomodulation in cancer treatment is to enhance the immune system's capacity to identify, target, and eradicate cancer cells. Conventional therapies including radiation, chemotherapy, and surgery have been the mainstay of cancer treatment for a long time. Even though these methods have shown great results in many situations, they frequently have drawbacks and can have serious adverse consequences. A viable substitute is immunomodulation, which strengthens the body's defences against cancer naturally.Adoptive cell treatments and immune checkpoint inhibitors are the two main types of immunotherapies for cancer As previously mentioned, immune checkpoint inhibitors specifically target molecules or pathways that control the immune response, allowing the immune system to more effectively identify and combat cancer cells. Conversely, adoptive cell therapies entail the modification or reprogramming of the patient's immune cells to enable them to identify and selectively target cancer cells. With the discovery of immune checkpoint inhibitors, such as PD-1/PD-L1 and CTLA-4 inhibitors, immunomodulation made significant progress.

These inhibitors have been remarkably effective in treating a variety of cancer forms, such as bladder cancer, lung cancer, and melanoma.
Some patients have seen long-lasting and even durable responses, which has led to a paradigm change in the treatment of cancer. Even in cases of advanced cancer that were though incurable, immunomodulation in cancer treatment has demonstrated great potential. The body's immunological response to cancer can be strengthened and harnessed, opening up new avenues for better patient outcomes and life quality. A major development in oncology, immunomodulation in cancer offers a fresh strategy to fight the illness. These treatments have the power to alter the course of cancer treatment and increase the survival rates of cancer patients by modifying the immune system. Further developments and study in this area could lead to significant breakthroughs in cancer immunotherapy.

2. Immunomodulators

Drug therapies known as immunomodulators alter the body's immune response to improve its efficiency. These consist of therapies that either boost or suppress your immune system. Immunodulators are used to treat autoimmune illnesses and cancer, among other ailments.
Both immunostimulatory and immunosuppressive drugs are considered immunomodulators, also known as biological response modifiers. The immunomodulators that are currently in use are represented by microbial products, agents of both natural and synthetic origin, and proteins produced from the immune system. Immunological cell's enhancement of anti-infectious immunity and the

development or restoration of immunological effector activities are two aspects of immunoenhancer's mechanisms. Immunosuppressive agents, immunomodulators are the three primary categories of agents that immunomodulators affect [1,2].

2.1 Immunosuppressants Agents

Two immunosuppressive medications that are presently being researched are repamycin and FK506 [3]. Additional agents are not within the scope of this work and will not be considered. FK 506 functions as a macrolide immunosuppressant, much like cyclosporine. FK 506 is at least 100 times more effective than ciclosporin at precisely preventing the release of IL-2, IL-3, IL-4, and interferon in response to different stimuli, according to helper T cell in vitro tests. Additionally, FK 506 might lessen the expression of IL-2 receptors on T cells that nonself-antigens have activated. Although the precise molecular mechanism of action of FK 506 is uncertain, it prevents early, calcium-dependent steps in signal transduction that frequently follow T cell stimulation[4].

FK 506 may be more effective in liver transplantation because of its stronger hepatotropic qualities compared to ciclosporin. Eight centers in Europe have started a prospective randomized research comparing FK506 with ciclosporin immunosuppression in liver transplantation, while multicenter study including more than 650 liver graft patients is currently in progress in North America. Nephrotoxicity is one of the common side effects of ciclosporin and FK 506 in humans. On the other hand, no reports of hirsutism, gingival hyperplasia, or coarsening of facial characteristics have been made for506 [4].
A potent immunosuppressant begin studied in animals is rapamycin. Its somewhat complicated mode of action is different from FK 506's. Similar to FK 506, dogs are particularly hazardous to rapamycin. Rapamycin-induced vasculitis, on the other hand, is primarily limited to the gastrointestinal tract, while FK 506-associated vasculitis affects the heart and is more widely distributed. Most likely, this effect is species-specific [5].

2.2 Immunostimulating Agents

The most significant immunostimulant is the BCG vaccine. Recurrent superficial bladder cancer is treated with topical BCG [6]. One possible method of action could be a T cell response that is constrained by HLA. There is convincing evidence that treatment causes cancer cells to produce the HLA class II antigen, and there is a direct relationship between the amount of IL-2 secreted into the urine and the response to treatment. Topical BCG is being studied for the treatment of melanomas and head and neck tumors.
An artificially produced oral active medication with anthelmintic and imunomodulatory qualities is levamisole. Patients with surgically removed stage C colon cancer have been shown to have a one-third lower chance of mortality and recurrence when levamisole and fluorouracil are taken together. Its complicated and still unclear how levamisole influences the immune system in humans. Most in vitro and in vivo studies point to levamisole's role as an immunorestorative medication. It can strengthen a weakened host immune system, but it can't overstimulate a healthy system. Granulocytopeni is the most severe side effect linked to levamisole[7].

Table 1: Cytokines

Name of group (abbreviation)	Subcategories	Other names
Colony-stimulating factors (CSF)	G-CSF GM-CSF M-CSF Multi-CSF	Neupogen® Leucomax IL-3
Interleukins (IL) to proleukin®	IL-1 IL-2 IL-4 IL-5 IL-6 IL-7 IL-8 up to	Factor 1 that stimulates B cells Factor boosting B cell II
Interferons (IFN)	IFN-α 2a IFN-α 2b INF-β INγ	Roferon-A® INF-βINγ
Tumor Necrosis Factors (TNF)	TNF-α TNF-β	Cachectin Lymphotoxin

3. Immune Response

In addition to providing the body with defense systems against most microbes, the immune system also enables the body to respond precisely and precisely to a particular invader. The immune system responds in two ways: innately, which is non-specific, and adaptively, which is highly specialized. The intrinsic reaction, often our first line of defense against anything foreign, allows the body to always defend itself against a sickness in a similar way. Examples of these natural processes include the reticuloendothelial system, the skin barrier, tears, saliva, various cytokines, complement proteins, lysozyme, bacterial flora, and a range of cells, including neutrophils, basophils, eosinophils, monocytes, macrophages, NK cells, and platelets.The adaptive acquired immune response will make

advantage of certain cell's capacity to produce an immune response against the invasive bacteria, as well as their byproducts (cytokinase and immunoglobulins). These are some of its characteristics: [8,9,10].

a. Specificity: as a result of the triggering mechanism being a particular illness, immunogen, or antigen.

b.Heterogeneity: the production of unique immune response effectors against millins of foreign invaders is known as heterogeneity.

c.Memory: on its second encounter with the virus, the immune system is able to identify it and mount a more potent and quick defense.

An illustration of innate immunity is the inflammatory immune response, which prevents invasive microorganisms from entering the body through the cutaneous, respiratory, or digestive systems. When infections manage to get beyond the epithelium surfaces, they come into contact with macrophages in the subepithelial tissues, which will try to swallow them and also release cytokines that will intensify the inflammatory reaction.

4. Types of Immunomodulators

Immunomodulation in cancer refers to the use of several strategies to modify or enhance the immune system's response to malignant cells within the body. Immunomodulatory treatments have garnered a lot of interest in the field of cancer research due to their promising results in the treatment of cancer. This review aims to discuss the many immunomodulatory strategies that have been established for cancer treatment [11].

4.1 Immune Checkpoint Inhibitors

Immune checkpoint inhibitors (ICIs) are a unique class of antineoplastic antibodies that disrupt the inhibitory coreceptors on T cells. There are now two types of immune checkpoint receptor antibodies that target either the cytotoxic T lymphocyte associated protein 4 (CTLA-4) pathway or the programmed cell death (PD-1) pathway. In landmark clinical trials, the anti-CTLA-4 antibody ipilimumab achieved remarkable malignant remissions in metastatic melanoma in 2010 [12]. Immune checkpoint inhibitors, either alone or in combination, have rapidly become the gold standard in the treatment of a variety of malignant tumor types, including non-small cell lung cancer and urothelial cancers, as well as molecular tumor phenotypes like deficient mismatch repair (dMMR) and high microsatellite instability (MSI-H) [13].

Many patients have immune-related adverse events (irAEs) during ICI treatment, which are caused by immunological activation and can impact almost all organ systems. There has been substantial overlap in the reported different toxicity of ICIs. All things considered, adverse events linked to anti-CTLA-4 medications. Combining these two groups of drugs generally results in the highest level of toxicity [14].

4.2 Adoptive Cell Therapy

Adoptive cell therapy is a cancer treatment that uses gene editing to enable T lymphocytes to recognize and destroy cancer cells. By modifying ACT, the immune system can be enhanced or modified to some degree, which can be applied to more successfully treat cancer. TCR-T treatment can be used in preclinical research because of the structure and function of the TCR. T lymphocyte receptors (TCRs) have multiple functions in the immune response. For example, TCRs in regulatory T cells and cytotoxic T cells help destroy cancerous or infected cells, while TCRs in regulatory T cells help regulate responsiveness. These cells specificity is likewise regulated by the TCRs [15]. ACT entails harvesting immune cells from the patient's peripheral blood or the tumor itself, isolating the cells ex vivo, and reinfusing the patient with activated T cells [16, 17]. T cells for controlled expression of the chimeric receptor (CAR), which fuses the TCR's signalling mechanism with the extracellular domain of the antibody. Furthermore, this strategy makes use of DCs, which are antigen-presenting cells that are very good at triggering T-cell response [18, 19, 20].

4.3. Monoclonal Antibody Therapy

B-lymphocytes become active in response to foreign material entry, and antibodies are made to identify the foreign material. Antibodies recognize the epitope regions on the antigen. An antibody that is produced against a single epitope as opposed to the entire epitope is known as a monoclonal antibody (mAb) [23,24].Monoclonal antibodies are the most commonly utilized and authorized kind of cancer immunotherapy in clinical practice. mAbs mainly target colon, breast, and other cancer types in addition to lymphomas [25]. However, there are a variety of side effects associated with the use of mAbs, such as fever, trembling, weariness, headache, stiffness in the muscles, nausea/vomiting, rash, and bledding [26].

4.4. Cancer Vaccines

Cancer vaccines work by altering immune system cells to combat cancer cells. Creating in vivo tumor-specific or tumor reactive immunoreactivity is the aim of cancer vaccinations. The most prevalent form of vaccines, which are peptide-based, are composed of immunogenic epitopes from tumor-specific or tumor-associated antigens [21, 22]. Adjuvants are typically administered in conjunction to vaccines are a good substitute for active immunotherapy in the treatment of cancer since they use the patient's own immune system to treat advanced disease [19].Therapeutic cancer vaccines aim to immunize patient's own immune

systems in order to produce anticancer T cells. The medical sciences face significant obstacles in providing effective, safe, and long-lasting cancer treatment. One promising strategy for inducing protective antitumor immunity over the long term is the use of therapeutic cancer vaccines [25, 27]. The fact that these studies constitute the foundational research on monoclonal antibodies used in cancer treatment is one of its major advantages [28,29].

4.5. Interferon Therapy

Proteins called interferons are members of the class of signalling molecules called cytokines, which are involved in the immune response's upregulation. While interferons are very crucial in the battle against viral infections, they are also essential in the suppression of tumors, the overexpression of MHC class 1 and 2, signal transmission, and the activation of immune cells such as macrophages and natural killer cells. Interferons can be roughly categorized into three basic subtypes: type 1 interferon subclass includes interferon-alpha and beta, whereas type 2 interferon subclass includes interferon-gamma [30]. Interferon lambda is a member of type 3 , the third subclass of interferons that was found more recently [31].

5. Biologics

A class of medicinal substances known as biologics is used to treat a variety of diseases. These medicines are generated from living things, such as cells or tissues [32]. The capacity of biologic medicines to target certain proteins or pathways implicated in the course of illness progression is one of its main benefits. For instance, one sort of biologic called a monoclonal antibody can be engineered to attach to particular receptors on the surface of cancer cells, obstructing the cell's ability to grow, and inducing an immune response against the tumor. This focused strategy avoids harm to healthy cells and lessens the need for conventional treatments like chemotherapy [33].

Types include:

5.1. Tumor necrosis factor (TNF) inhibitors

The cytokine tumor necrosis factor, or TNF, is vital for inflammation and immune responses. Numerous immune cells, including macrophages, generate it, and it serves as a signaling molecule that regulates the recruitment and activation of immune cells. However, an excess of TNF production can cause tissue damage and persistent inflammation in conditions including psoriasis, inflammatory bowel disease, and rheumatoid arthritis. The development of TNF inhibitors has been a key development in the treatment of various inflammatory diseases. TNF inhibitors are biologics that specifically target TNF and prevent its binding to receptors on immune cells. These inhibitors the inflammatory cascade and reduces the symptoms and progression of the disease. Examples of TNF inhibitors include adalimumub, infliximub, and etanercept [34].

5.2. Interleukin-1

Another significant cytokine implicated in inflammatory processes is interleukin-1. It helps to activate immune cells and produce other inflammatory chemicals when it is released in reaction to an infection or injury. Many autoimmune and auto-inflammatory diseases, such as gout, rheumatoid arthritis, and recurrent fever syndromes, have been linked to excessive IL-1 production [35]. Biologics drugs known as IL-1 inhibitors specifically target and inhibit the activity of IL-1. They lessen inflammation and improve the discomfort brought on by these illnesses. Anakinra (kineret®), a medication used to treat rheumatoid arthritis and other auto-inflammatory disorders, is an illustration of an IL-1 inhibitor [36].

5.3. T cell inhibitors and B cell inhibitors

Biologic medicines known as T cell inhibitors and B cell inhibitors target T cells and B cells, respectively, which are important participants in immunological responses. T cell inhibitors, like ustekinumab, and abatacept, control T cell activation and proliferation, which lowers inflammation in diseases including psoriasis and rheumatoid arthritis. However, B cell inhibitors, like ocrelizumab and rituximub, target and deplete B cells, which are linked to autoimmune illnesses including multiple sclerosis and rheumatoid arthritis and are implicated in the creation of autoantibodies [37].

6. Conclusion

In the field of oncology, immunomodulation in cancer has become a ground-breaking strategy. Immunomodulatory medicines have shown considerable promise in efficiently and killing cancer cells by utilizing and boosting the body's natural immune response. Two important classes of immunotherapies that have demonstrated exceptional efficacy in treating a variety of cancer types are immune checkpoint inhibitors and adoptive cell treatments.By relieving the immune system of its constraints, immune checkpoint inhibitors, such CTLA-4 and PD-1/ PD-L1 inhibitors, have completely changed the way cancer is treated. These inhibitors have demonstrated encouraging outcomes, producing robust and long-lasting reactions. Moreover, adoptive cell therapies have demonstrated notable effectiveness in treating some cancer types, such as

pediatric acute lymphoblastic leukemia, by reprogramming or changing the patient's immune cells to selectively target cancer cells.Immunomodulation has not only restored hope for cancer patients, but it has altered the course of cancer treatment. Conventional therapies, like radiation, chemotherapy, and surgery, have numerous limitations and can have grave side effects. Immunotherapies offer a more targeted and potentially safer approach to cancer treatment. Additionally, immunomodulatory methods have been successful in treating advanced malignancies that were previously thought to be incurable, giving patients who had fewer therapy options more options.

7. Summary

One important development in the fight against cancer is immunomodulation. These treatments have the ability to greatly enhance patient outcomes and quality of life by modifying the immune system. Further developments in cancer immunotherapy could result in more effective and individualized treatment options for cancer patients, so long as research and development in this area are sustained.

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