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Cancer Immunotherapy: Clinical Applications, Challenges and Future Directions

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Introduction:

In 1893, Dr. William B. Coley had a sarcoma patient in which he found it impossible to remove the tumor entirely via surgery, at the time this patient's case would've been thought of as hopeless as modern cancer treatments such as chemotherapy and radiotherapy were not invented yet. But Dr. Coley managed to cure the sarcoma patient by inducing a severe bacterial infection. His use of toxins later known as Coley toxins is widely regarded as the first case of cancer immunotherapy [1].

Following this, cancer treatment in the 20th century was mainly in the form of surgery, radiotherapy, and chemotherapy. These approaches aim to eliminate cancerous cells through physical removal or non-specific cytotoxic treatments. However, while these treatments have improved survival chances in many cancer types, they have adverse side effects and cause damage to both healthy and cancerous cells. Moreover, these approaches fail to prepare the patient for future encounters with cancer [2].

On the other hand, cancer immunotherapy follows a different approach. Instead of directly attacking cancerous cells, cancer immunotherapy aims to activate the immune system so that the body would recognize the cancerous cells and eliminate them on its own. By targeting immune pathways or using engineered immune cells, immunotherapy ensures a much more specific treatment than any other type of cancer therapy. Moreover, immunotherapy provides the patient with long-lasting immune memory which will help them in any future encounters with cancer [2].

To elaborate, recent advances in immunology and biotechnology have improved scientists' understanding of the immune system as a whole and allowed for the development of new and more precise immunotherapy strategies. These include immune checkpoint inhibitors (ICIs), adoptive cell transfer such as chimeric antigen receptor (CAR) T-cell therapy, cancer vaccines, and oncolytic viruses. These approaches have shown clinical success in treating cancers that were previously tough to treat. Yet, immunotherapy is not perfect and has its flaws such as immune-related side effects, high cost, and limited access [2].

This research paper aims to take a deeper look into the current applications of immunotherapy, their mechanisms of action, as well as the challenges immunotherapy is facing. It also aims to highlight strategies that may help improve its effectiveness and accessibility.

Historical Development and Milestones:

Immunotherapy can be traced back to the late 19th century when Dr. William Coley realized that tumors sometimes regressed when they were faced with bacterial infections. Based on this observation, he developed the idea of injecting a mixture of bacteria and toxins, known as Coley's toxins, directly into tumors. This approach was correlated with tumor regression, however, it also caused significant toxicity and adverse effects in patients, limiting its use. Later, Dr. George Dock also observed that cancer patients who contracted influenza showed enhanced immunity against tumors. This further supported the idea that immune activation could play a role in combating cancer. In addition, the immune surveillance theory emerged, originally proposed by Dr. Paul Ehrlich, who suggested that the immune system can detect and eliminate emerging cancer cells through specific cell surface markers, which we now recognize as HLA and other tumor-associated markers. In 1949, Frank Burnet and Lewis Thomas formulated the cancer immune surveillance hypothesis, proposing that the immune system distinguishes self from non-self and recognizes malignant cells as abnormal. This theory was later supported by the discovery of T cells, natural killer cells, and tumor-specific antigens. Another important milestone was the use of cytokines in immune activation.

In 1959, Dr. Lloyd Old, Benacerraf, and Clark demonstrated that the BCG vaccine could stimulate immune-mediated tumor killing in mice. This therapy was later approved by the FDA in 1994 for bladder cancer. Tumor necrosis factor was discovered in 1975 and shown to cut off blood supply to tumors, leading to tumor cell death, but its use was limited due to severe toxicity. Interleukin-2 (IL-2), identified in 1976, promoted T-cell expansion and proliferation and induced complete remissions in metastatic melanoma. It received FDA approval for renal cell carcinoma and melanoma, although its use was also restricted by toxicity. These findings established that immune cells could eradicate advanced cancer. In addition, a major breakthrough came with immune checkpoint inhibitors. Molecules such as CTLA-4 and PD-1 normally suppress immune responses.

Dr. James Allison and Dr. Tasuku Honjo developed inhibitors such as ipilimumab and pembrolizumab to block these checkpoints, releasing T cells to attack cancer. Their work earned them the Nobel Prize in Medicine in 2018. Additional advances include cancer vaccines, oncolytic viruses, adoptive cell therapies such as CAR T-cell therapy, cancer-preventive vaccines like HPV and hepatitis vaccines, and modern combination therapies, including bispecific antibodies such as blinatumomab, approved in 2017. [6]

Interest in immunotherapy declined after Coley due to inconsistent results, safety risks, poor understanding of immunology, and the rise of more predictable treatments like radiation and chemotherapy. However, interest resurged after advances in immunology, biotechnology, and clinical successes revealed how the immune system can be precisely harnessed to treat cancer. [7]

Mechanisms of Action:

There are several mechanisms of action in immunotherapy, which are inhibition (checkpoint inhibitors), adoptive cell transfer, and CAR-T cells.

First, immune checkpoint inhibition: in our immune system, there are certain checkpoints like PD-1 and CTLA-4, which act to inhibit immune system activity, stopping T cell proliferation, and preventing them from attacking cancer cells. Scientists have been able to make anti-CTLA-4 and anti-PD-1 antibodies in order to block these inhibitory checkpoints, allowing T cells to proliferate and attack cancer cells. [8]

Furthermore, adoptive cell therapy is an immunotherapy technique in which T-lymphocytes of the body that are specific to tumors and act to kill them are taken from the patient, after which they are proliferated and expanded ex vivo, and then allowed to proliferate in vivo after reinjection into the patient to stimulate tumor regression. ACT is most commonly done by using autologous tumor-infiltrating lymphocytes, which have given the highest clinical efficiency among immunotherapies for metastatic melanoma. However, early limitations of ACT were present, as there was poor persistence of transferred cells, but these were overcome by using lymphodepleting preparative regimens before cell transfer.
Lymphodepleting regimens increase ACT efficiency by removing regulatory T cells and reducing competition for homeostatic cytokines, including interleukin-7 and interleukin-15, which allows the T cells to expand and function in vivo. Clinical responses strongly correlate with T-cell persistence, proliferative capacity, and telomere length. In addition, ACT can induce durable and consistent tumor regression across several metastatic sites, including the brain. Also, advances in genetic engineering enabling tumor-specific T-cell receptor expression have extended ACT to cancers that do not have naturally occurring tumor-reactive lymphocytes in the body. This has made ACT a foundation for modern engineered T-cell therapies. [9]

Moreover, another mode of action of immunotherapy is using CAR-T cells. Similar to adoptive cell transfer, lymphocytes are collected from a patient's blood. However, instead of allowing their expansion in vivo, scientists genetically modify them by adding a chimeric antigen receptor (CAR). This allows the cells to recognize a specific tumor antigen through the antibody fragment scFv, which activates the T cells. Once activated, the CAR-T cells can directly kill the tumor, recruit other immune cells, or release cytokines to stimulate an immune response, leading to tumor regression. After the infusion, patients are monitored for side effects and for the persistence and activity of the CAR-T cells. CAR-T therapy has demonstrated significant clinical success in blood cancers such as leukemia and lymphoma. [10]

Techniques:

There are multiple techniques that are used to apply immunotherapy, and these include cancer vaccines and oncolytic viruses. Cancer vaccines are a type of immunotherapy designed to stimulate the immune system and help it target antigens of cancer cells. Unlike preventive vaccines which are given before the disease enters the body and aim to prepare the body to fight off the disease, cancer vaccines are therapeutic and are given after discovering cancer, thus they aim to enhance the antitumor response [3]. These vaccines mainly operate by activating dendritic cells which prime T-cells to attack cancerous cells [2].

Cancer vaccines are classified into multiple categories which include protein or peptide vaccines, DNA or RNA vaccines, dendritic cell-based vaccines, and whole-cell vaccines [2]. Protein or peptide vaccines work by introducing tumor specific or tumor related antigens to the body to induce an immune response, however their clinical effectiveness is limited due to immunogenicity and the tumors' ability to evade immune detection [4]. While Dendritic vaccines aim to avoid these problems by directly presenting the antigens to the dendritic cells in vitro then reintroducing the dendritic cells to the body, therefore enhancing the antigen presentation and T-cell activation [2]. On the other hand, DNA and RNA vaccines work by injecting DNA or RNA holding the information of cancerous antigens into the patient, then dendritic cells near the injection site take the genetic material and produce the antigens encoded in the material. In other words, dendritic cells produce cancerous antigens to show to T-cells, and these T-cells attack and lyse cancerous cells [3]. Furthermore, whole cell vaccines use complete cancer cells or cell types to trigger an immune response; by presenting multiple antigens at once, whole cell vaccines aim to reduce the risk of immune escape [4].

Despite their theoretical promise, cancer vaccines often fall short in clinical trials due to several reasons such as self-tolerance, tumor heterogeneity, antigen loss and the immunosuppressive environment of the tumor [4,5]. Thus, current research efforts are focused on improving the efficacy of vaccines through combining strategies. Vaccines are tested in combination with immune checkpoint inhibitors, cytokines, or other immunomodulatory agents to try and enhance immune activation and overcome the immunosuppressive nature of tumors [5]. And research into personalized patient-specific vaccines targeting specific tumors that develop in patients lead to more selective immune responses [4]. Despite the challenges, cancer vaccines remain an important tool in the immunotherapy arsenal.

Oncolytic viruses are a type of immunotherapy that works by injecting genetically modified or naturally occurring viruses that target cancer cells into the patient to selectively infect and kill cancerous cells and spare normal cells. This works because cancer cells have impaired antiviral defense such as impaired interferon signaling, thus it is much easier for a virus to replicate in them than healthy cells. As the virus continues to replicate in tumor cells until the cells become so full that they lyse or burst, leading to direct tumor cell death [2,3].

In addition to their direct tumor cell death, oncolytic viruses stimulate the immune system's antitumor response. Tumor cell lysis leads to the release of more viruses to eliminate more tumor cells, as well as the release of tumor antigens and damage-associated molecular patterns, which are essentially danger signals that cause inflammation and recruit dendritic cells to the area of lysis. And just like in cancer vaccines, the dendritic cells process the tumor antigens and present them to T-cells which are then activated. This forces a change in the cancerous environment from immunologically inactive or immunosuppressed, to immunologically active where cytotoxic T cells can recognize the tumorous cells and destroy them [5].

Many oncolytic viruses have been developed using different viral platforms, including herpes simplex virus (HSV), adenovirus, vaccinia virus, and reovirus. The first oncolytic virus to be FDA approved is the T-VEC (Talimogene Laherparepvec) which was approved for use against metastatic melanoma. It is a modified Herpes Simplex Virus type 1, designed to replicate within tumor cells and codes for a protein GM-CSF which helps the immune system recognize the tumor cells [5]

Despite their promise in preclinical trials, oncolytic viruses face a few challenges when used in clinical trials. These challenges include rapid clearance of the virus from the body by the immune system, in addition to limited effectiveness as monotherapies against solid tumors [2]. Which is why modern research is focused on combination therapies, specifically on the use of oncolytic viruses with immune checkpoint inhibitors to enhance T-cell activation [5]. Overall, despite the challenges they are currently facing, oncolytic viruses remain a unique immunotherapeutic tool that utilizes both direct cell lysis and immune system activation.

Clinical Application and Case Studies:

Starting in the 21st century, immunology has increasingly been translated into real clinical practice, leading to numerous documented cases of success despite the significant challenges faced in the field.

One prominent example involves a group of 19 children treated for neuroblastoma, a rare solid tumor, using CAR T-cell therapy. Although many patients experienced relapse and ultimately did not overcome the disease, two children with active cancer achieved complete remission following treatment. Remarkably, one of these patients has remained cancer-free for more than 18 years, representing the longest recorded sustained remission following CAR T-cell therapy for a solid tumor. What was even more surprising was that the woman who remained cancer-free for 18 years went on to have two successful full-term pregnancies with no birth complications or apparent disorders in the newborn, showcasing the limited long-term toxicity of CAR T-cell therapy. Overall, this research displayed the long-term persistence and durability of CAR T-cells, as well as the sustained effectiveness of this therapeutic approach. Importantly, it showed a potential benefit of CAR T-cell therapy in how it does not decrease over time, but

may instead increase as immune surveillance sharpens. [1] In another study, Maureen Sideris, a 71-year-old woman diagnosed with gastroesophageal junction cancer, was initially told that surgery was unavoidable and could leave her unable to speak normally or eat solid foods. Instead, she enrolled in a clinical trial testing an immunotherapy drug for patients with a rare cancer subtype. She received nine intravenous doses over six months, after which her tumors gradually decreased in size and eventually completely disappeared.

In this trial, researchers at Memorial Sloan Kettering Cancer Center administered dostarlimab, a PD-1 immune checkpoint inhibitor, in 117 patients with mismatch repair–deficient (MMRd) tumors, which arise due to defects in DNA repair mechanisms that lead to an accumulation of mutations. The results were highly encouraging, with approximately 80% of patients achieving complete tumor eradication without the need for surgery.

When this therapeutic approach was tested on other MMRd tumors—such as those affecting the stomach, esophagus, liver, and urinary tract—35 out of 54 patients achieved complete tumor disappearance, although effectiveness varied depending on the cancer type.

These findings suggest that immunotherapy has the potential to become a first-line treatment, replacing or reducing reliance on traditional therapies such as chemotherapy, surgery, and radiation, which are often associated with severe side effects. Importantly, the use of immunotherapy did not compromise patient outcomes, as delayed surgical intervention, when necessary, produced results comparable to early surgery.

However, immunotherapy is not suitable for all patients, and ongoing research aims to expand its effectiveness across a broader range of cancer types and patient populations. [2] In another study, a patient with stage IVa advanced lung adenocarcinoma developed resistance to osimertinib, a third-generation EGFR-tyrosine kinase inhibitor administered as immunotherapy drug in order to stimulate an immune response. To treat him, doctors administered antigen-specific cytotoxic T-lymphocyte (ACTL) therapy, a type of adoptive cell therapy in which the patient's T cells are modified and expanded in the lab to target cancer cells. This treatment led to complete tumor regression, achieving a clinical complete response (cCR) that was maintained for six years. This was the first reported case of ACTL curing lung cancer, demonstrating the potential of ACT to overcome drug resistance and serve as a powerful alternative or complement to surgery, radiation, and chemotherapy. [3]

Limitations and Challenges:

Despite its outstanding potential and substantial achievements, immunotherapy still faces many challenges and limitations which restrict its effectiveness and clinical application. One of the most significant challenges immunotherapy is facing is the variability in patient response. Even though some patients experience long lasting benefits, others might not even experience

any. These mixed results are mainly due to differences in tumor biology, immune system function, and the tumor microenvironment [2].

Moreover, another major limitation would be the development of primary and acquired resistance to immunotherapy. As some tumors are inherently resistant to immunotherapy which might be due to multiple factors like immunogenicity, absence of tumor-infiltrating lymphocytes, or impaired antigen presentation. While other tumors might initially respond to immunotherapy then fail to respond, which might be due to antigen loss, meaning that the patient has more than one type of mutations in his body, each one displaying certain antigens, and some of these types of mutations are destroyed by immunotherapy, which leaves the others resistant to immunotherapy through natural selection. Other types of resistance include upregulation of alternative immune checkpoint pathways and immunosuppressive signaling within the tumor microenvironment [3]. These resistance mechanisms greatly reduce the long-term efficacy of immunotherapy.

Another current challenge that immunotherapy is facing is immune-related adverse events (irAEs). Immune-related adverse events are a category of side effects that happen when immunotherapy over activates the immune system and causes it to attack healthy tissues. In a healthy body, immune checkpoints like CTLA-4 or PD-1 act as brakes to stop the body from attacking itself, but immunotherapy like immune checkpoint inhibitors remove these checkpoints to allow the immune system to attack the tumor cells, but this might backfire and make the body attack itself which leads to irAEs [12]. The most affected organs include the skin, gastrointestinal tract, endocrine glands, lungs, and liver [5]. Although most irAEs can be treated with immunosuppressors, some cases can be very severe and require treatment discontinuation [12]. This side effect shows the delicate balance between effective anti-tumor therapy and immune toxicity that immunotherapy tries to exploit.

Furthermore, the immunosuppressive microenvironment of tumors further limits the effectiveness of many of the immunotherapeutic techniques and mechanisms. This is because tumor cells can release immunosuppressive cytokines and recruit myeloid-derived suppressor cells as well as cause alterations such as hypoxia and nutrient depletion. These mechanisms of tumor cells impair the capabilities of T-cells and make it difficult for the T-cells to infiltrate the tumor microenvironment, which significantly reduces the effectiveness of treatments that rely on immune activation such as cancer vaccines and adoptive cell transfer [5].

Moreover, biological challenges are not the only challenges that stand in the way of immunotherapy, as there are economic and logistic challenges that face immunotherapy as well. In fact, treatments such as CAR-T cell therapy are highly complex and require patient specific cell manufacturing in specialized facilities, as well as a lot of intensive clinical monitoring. This results in a very high cost of treatment which limits accessibility. Even common checkpoint

inhibitors are expensive, which raises questions about the long-term sustainability and patient access of immunotherapy [2].

Collectively, these challenges that face immunotherapy show that even though immunotherapy has been revolutionary in the field of oncology, we are still a long way from realizing its full potential. Further research tackling resistance mechanisms, minimizing toxicity, improving patient selection, and reducing cost is essential for immunotherapy to become a viable treatment for cancer.

Future directions and emerging strategies:

As cancer immunotherapy continues to evolve, current research is focused on improving treatment efficacy, reducing toxicity, and increasing accessibility. The most promising areas of research are those that focus on combination strategies that integrate multiple complementary immunotherapeutic strategies and mechanisms to improve overall treatment results. Combining immune checkpoint inhibitors with cancer vaccines, oncolytic viruses, chemotherapy, or radiotherapy has shown the potential to enhance antitumor immune response by increasing tumor antigen release and overcoming immune resistance mechanisms [3,5].

Another promising area of research is the identification of predictive biomarkers of tumors. More precise biomarkers could enable better patient selection and improve treatment decisions, which should lead to more effective treatment and minimize unnecessary toxicity. Like PDL-1 and tumor mutational burden, researchers are looking into other biomarkers such as immune gene expression patterns, circulating tumor DNA, and features of the tumor microenvironment. These markers may provide a more accurate depiction of how the tumors interact with the immune system, which should help predict the response of tumors to immunotherapy [2].

Furthermore, research into personalized neoantigen vaccines is another emerging strategy that should help increase the effectiveness of immunotherapy. Unlike older vaccines that focus on general antigens found in many cancer types, these vaccines are patient specific and target the specific neoantigens of the tumor in the patient. By focusing on patient-specific neoantigens, these new vaccines can reduce side effects and enhance immune specificity. Early clinical trials have shown promising potential, yet large scale validation is still required [4,5].

Moreover, research into adoptive cell therapies is also being refined to improve safety, durability, and applicability. Novel CAR-T designs, including dual-target CARs, armored CAR-T cells, and allogeneic “off-the-shelf” products, aim to address current limitations such as antigen escape, toxicity, and manufacturing complexity. Additionally, new cell types other than CAR-T cells are being explored for their potential in immunotherapy, including natural killer cells, which broadens the therapeutic options [3].

Finally, research aimed at reducing toxicity and improving accessibility is essential for the long-term success of immunotherapy. Strategies such as localized delivery, controllable immune activation, and cost-reducing manufacturing processes are actively being explored. These emerging approaches suggest that the future of immunotherapy will be more personalized, effective, combination-based, and widely accessible to patients around the globe [2].

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