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REVIEW ARTICLE

Cancer Immunotherapy: A Systemic Review

Sujal Kumar Bokshi[1], Kakoli Rani Biswas[2], Ashesh Chowdhury[3]

[1]MBBS, MPhil (Immunology), MO in Charge of Pathology and RMO, District Hospital, Narail, Bangladesh.
[2]B. Pharm, M. Pharm, Khulna university, Khulna, Bangladesh.
[3]Professor and Head of Department of Immunology, BIRDEM, Dhaka, Bangladesh.

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Corresponding Author: Sujal Kumar Bokshi, MBBS, MPhil (Immunology), MO in Charge of Pathology and RMO, District Hospital, Narail, Bangladesh.

Abstract

This review examines immunotherapy, a method that uses the immune system to fight cancer, focusing on treatments like CTLA-4 and PD-1/PD-L1 inhibitors, and CAR-T cell therapy. It discusses the effectiveness of these therapies in enhancing the immune system's ability to detect and destroy cancer cells. Additionally, the role of antibodies, vaccines, and cytokines in cancer treatment is explored. Emphasizing the need for individualized treatment plans, the review suggests that customizing therapy to each patient's specific condition could lead to improved outcomes and fewer side effects. The aim is to highlight the potential of immunotherapy as a valuable cancer treatment option and advocate for more personalized approaches in patient care.

Keywords: Immunotherapy, Cancer Treatment, CAR-T Cell Therapy, PD-1 Inhibitors, Personalized Medicine.

1. Introduction

Cancer arises from the abnormal growth of cells due to multiple alterations in gene expression, disrupting the balance between cell proliferation and cell death. Over time, these changes lead to the development of a population of cells capable of invading surrounding tissues and spreading to distant sites, a process known as metastasis. This progression can result in considerable illness and, if not addressed, may ultimately lead to the death of the affected individual [1]. In Bangladesh, out of a population of 142 million individuals, there are an estimated 1.3 to 1.5 million individuals living with cancer, and approximately 200,000 new cases are diagnosed each year [2]. For many years, conventional cancer treatments have involved the use of chemotherapy drugs and ionizing radiation to target and reduce the size of tumors. While these treatments have provided significant benefits and even led to some cures, a major challenge is the recurrence of tumors, often due to the emergence of drug-resistant mechanisms within certain tumor cells with some complications [3]. Consequently, there is a pressing need for the development of alternative therapeutic strategies to effectively eliminate tumor cells and improve treatment outcomesthat is more targeted, more effective and has less side effect.By stimulating the immune system to produce antitumor effects, cancer immunotherapy is becoming a useful strategy for the treatment of cancer [4].The concept of the immune system’s potential to recognize and eliminate cancer was initially proposed in the 19th century. However, tangible evidence of this principle was not readily available until later. A notable observation involved certain sarcoma patients experiencing tumor regression coinciding with the development of a skin infection caused by Streptococcus pyogenes. It was speculated that this infection might trigger an immune response against both the infection and

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the cancer cells. Subsequently, researchers used a combination of heat-killed S. pyogenes and Serratia marcescens (known as Coley's toxin) to treat sarcoma patients, leading to complete tumor regression in some cases. These early investigations with Coley's toxin spurred numerous clinical trials aimed at stimulating the immune system to combat cancer [5].Cancer development is fundamentally driven by somatic genomic changes, which occur sequentially and contribute to the progression toward increasingly aggressive and invasive tumor phenotypes. These genomic alterations can lead to the formation of tumor antigens, which are recognized by the immune system as foreign or non-self. Consequently, the immune system may mount cellular immune responses against these tumor antigens [6] On the other hand, one of the characteristics of cancer involves avoiding immune destruction [7].Cancer cells have developed various strategies, including impairments in antigen presentation, increased activation of negative regulatory pathways, and the recruitment of immunosuppressive cell populations, to evade detection and destruction by the immune system [8].Numerous studies have been conducted on the intricate and dynamic relationship between tumor cells and host immune cells, which has resulted in the development of immunotherapies that are now allowed [9].Immunotherapy aims to either directly target a particular antigen present on the tumor or boost the immune system of the host [10]. However, many early clinical studies failed due to a lack of knowledge of the molecular aspects of immune responses.This review covers all aspects of immunotherapy in depth and examines the literature on tumor immunity to help unravel the mysteries surrounding immunotherapy.

2. Immune Checkpoint Therapy

Specialized biological pathways have been adopted by cancer cells to promote the growth of the tumor microenvironment [11].One strategy used by tumor cells to assure their survival and growth is to avoid immune system checkpoints [12]. Immune system checkpoints play a role in overseeing autoimmunity and reducing collateral tissue damage caused by immune reactions through the regulation of both stimulatory and inhibitory signaling pathways [13]. In the process of tumorigenesis, the imbalance in checkpoint protein expression can lead to the abnormal activation of inhibitory checkpoint receptors, which in turn preventing T cells from identifying and eradicating tumorigenic cells [14]. Checkpoint inhibitors represent a type of immunotherapy that triggers T cell-mediated anti-tumor responses by specifically obstructing inhibitory checkpoint receptors that are susceptible to manipulation by cancer cells [4]. The main targets of clinical cancer immunotherapy include immune checkpoint receptors such as cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), programmed cell death protein 1 (PD-1), programmed cell death 1 ligand 1 (PD-L1), lymphocyte activation gene 3 (LAG-3), and T cell immunoglobulin and mucin protein 3 (TIM-3) [15].

2.1 Anti-Ctla-4 Therapy

CTLA-4 functions as an immune checkpoint present on activated T cells, serving to restrain T-cell responses. Essentially, uncontrolled T-cell reactions have the potential to harm healthy tissues and cells; hence, CTLA-4 plays a vital role in regulating T-cell responses and safeguarding against self-inflicted damage [16]. While this mechanism serves to safeguard normal cells, in the context of cancer, it can also shield cancer cells. Preclinical studies have convincingly shown that inhibiting CTLA-4 enhances anti-tumor immune responses, demonstrating the potential for therapeutic intervention in cancer treatment [17].In the late 1990s, ipilimumab became the first completely human monoclonal (IgG1) antibody (mAb) against CTLA-4 to be tested in clinical studies. Patients with melanoma, renal cell carcinoma (RCC), prostate cancer, urothelial carcinoma, and ovarian cancer showed impressive clinical responses and decreased tumor size in phase I and II studies [18].In both early and late-phase trials, ipilimumab has demonstrated consistent effectiveness against melanoma. The efficacy of anti-CTLA-4 in generating lasting clinical responses and even potentially curing certain cancer patients has paved the way for the emergence of a new field known as immune checkpoint therapy. This field has further evolved with the discovery of additional pathways involved in inhibiting T-cell activity [19].

2.2 Anti-PD-1/PD-L1 Therapy

Programmed death 1 (PD-1) is a member of the CD28/CTLA-4 family and is expressed on the surface of activated T cells, B cells, monocytes, dendritic cells (DC), and natural killer (NK) cells. Its role in inhibiting T-cell activity was initially demonstrated in the early 2000s. Unlike CTLA-4, PD-1 seems to suppress T-cell responses by disrupting T-cell receptor (TCR) signaling, which is a distinct mechanism from CTLA-4's inhibition of T-cell responses by competing with CD28 for binding to B7 molecules. PD-1 interacts with two ligands, PD-L1 and PD-L2, both of which

are equally capable of dampening T-cell responses [20]. Antibodies designed to target the interaction between PD-1 and PD-L1 have demonstrated favorable clinical responses across various tumor types. Nivolumab, the first monoclonal antibody (mAb) targeting PD-1, exhibited notable clinical efficacy in patients with unresectable or metastatic melanoma, non-small-cell lung carcinoma (NSCLC), metastatic renal cell carcinoma (RCC), and classical Hodgkin lymphoma [21].

2.3 Lymphocyte Activation Gene 3

LAG-3, also known as CD223, is a coinhibitory receptor present on various lymphoid cells, including activated T cells and regulatory T cells (Tregs). Its function involves inhibiting the killing activity of effector T cells by promoting immune suppression mediated by Tregs [22]. Simultaneous inhibition of LAG-3 and PD-1 has been demonstrated to enhance the immune activity of exhausted CD8+ T cells, thereby bolstering a robust antitumor response. This approach also offers an improved safety profile compared to treatments targeting CTLA-4, as evidenced by a notable reduction in the incidence of systemic toxicities [23]. Moreover, numerous clinical trials have validated the effectiveness of LAG-3 as a vaccine adjuvant in the context of melanoma and prostate cancer. Additionally, the combination of LAG-3 with chemotherapy has shown promise in the treatment of metastatic breast cancer in clinical settings [4].A recombinant soluble fusion protein of LAG-3 called Immuntep (IMP321) is presently being evaluated in two or more clinical trials. Patients with advanced solid tumors are being tested in a phase I investigation for another anti-LAG-3 relatlimab (BMS-986016), either as monotherapy or in combination with anti-PD-1 (nivolumab) (http://clinicaltrials.gov/).

2.4 T-Cell Immunoglobulin and Mucin Domain 3

TIM-3 is a cell surface receptor expressed on T helper 1 (Th1) cells, which interacts with galectin-9, a ligand that is overexpressed in breast cancers and melanomas [24]. In tumorigenic cells, the signaling pathway involving TIM-3 and galectin-9 serves to suppress Th1 cell immune responses by promoting T cell exhaustion [25,26]. Preclinical experiments have demonstrated that combined inhibition of TIM-3 and PD-1, similar to LAG-3, restores the T cell fatigue caused by TIM-3/galectin-9 in order to enhance the antitumor response and decrease tumor burden [25]. The promising outcomes of this new generation of immune checkpoint inhibitors hold the potential to expand the utilization of biological therapeutics for treating diverse cancer types and addressing the shortcomings in cancer immunotherapy. In a phase I/II trial, the safety and effectiveness of MBG453, an antibody targeting TIM-3, are being assessed both alone and in combination with anti-PD-1 in patients with advanced malignancies (http://clinicaltrials.gov/).

3. Adoptive Cell Therapy

Several clinical investigations have shown that reintroducing autologous lymphocytes into cancer patients, obtained either from their tumors or peripheral blood, can impede tumor progression. These early studies served as the foundation for adoptive T-cell therapy [27].In adoptive immunotherapy, antigen-specific T cells are isolated from either the peripheral blood or the tumor, followed by their clonal expansion and subsequent transfusion back into the host with the tumor. This approach has led to tumor regression and improved survival rates by augmenting the number of reactive T cells, providing enduring immune protection, and ensuring antigen specificity. However, this method is associated with high costs and requires specialized expertise due to its labor-intensive nature. Assuming that T cells are already sensitized to the tumor and are antigen-specific, they can be activated ex vivo in a polyclonal manner before being reintroduced into the patient. It is crucial to suppress the immune system before adoptive transfer to enhance the antitumor efficacy. Significant strides have been made in establishing adoptive T-cell therapy as a standard treatment for cancer, with numerous ongoing studies aimed at further advancing this approach [28].

3.1 Tumor-Infiltrating Lymphocytes (TILs)

Tumor-infiltrating lymphocytes (TILs), which were found to be mononuclear lymphocytes with a tendency to wrap around and penetrate tumors, are one type of transferred lymphocyte [29]. Tumor-infiltrating lymphocytes (TILs) were initially identified in resected melanomas and were found to comprise a mixture of both CD4 and CD8 T cells. The general procedure for autologous TIL therapy involves several steps: 1) the resected melanoma is fragmented through digestion, 2) each fragment is cultured in interleukin-2 (IL-2), promoting the proliferation of lymphocytes, which subsequently destroy the tumor, 3) once a pure population of lymphocytes is obtained, these cells are expanded, 4) following expansion, typically up to 1011 cells, the lymphocytes are infused back into the patient [30]. In metastatic melanoma, adoptive T cell transfer of TILs results in a 50%

cancer response rate and a 20% complete response rate; the latter corresponds to a 20% cure rate due to the relatively lasting nature of the responses. Until the FDA approved checkpoint modulators (anti-PD-1), which demonstrate a similar degree of response, TILs were the only treatment for patients with metastatic melanoma that was authorized. [31].Similarly, T cell transfer through modifications of T cell receptors has demonstrated promise, particularly in targeting prevalent tumorigenic mutations, such as Ras mutations. The significance of Ras mutations in cancer has been well-established and recognized for several years. As a result, Ras is regarded as an attractive target for cancer therapy due to its frequent mutation in cancer initiation. Moreover, these mutations typically occur early in tumorigenesis, leading to widespread expression across nearly all tumor cells. Mutations in KRAS, a common proto-oncogene that encodes for a small GTPase, are detected in approximately 13% of colorectal cancers and 45% of pancreatic cancers[32,33]. The most prevalent KRAS mutations are characterized as gain-of-function mutations referred to as "hot-spot" driver mutations, with one of the most frequent being the substitution of the amino acid glycine with aspartic acid at codon 12, designated as KRAS G12D [34,35]. Despite extensive research spanning decades, researchers and clinicians have yet to develop a drug or vaccine capable of effectively targeting the KRAS protein in humans [35]. Recent studies have suggested that lymphocytes could serve as a promising source of T cells for combating tumorigenicity. These T cells can be engineered to express T cell receptors that specifically target the mutations present in the patient's tumor [36].

3.2 Chimeric Antigen Receptor T-Cell (Car-T) Immunotherapy

CAR-T, or chimeric antigen receptor T-cell immunotherapy, is an effective form of adoptive cell therapy. It involves extracting T cells from the patient's body through leukocyte reduction procedures, genetically engineering them to express chimeric antigen receptors (CARs) on their surface, and then transferring them back into the patient's tumor site to target and kill tumor cells specifically. This therapy has demonstrated high remission rates in tumors expressing CD19 proteins, such as B-cell acute leukemia and large B-cell lymphoma. FDA-approved drugs in this category include Novartis's tisagenlecleucel-T (Kymriah) and Kite/Gilead's axicabageneciloleucel (Yescarta). Kymriah is approved for the treatment of recurrent or refractory B-cell acute lymphoblastic leukemia [37]. Yescarta is indicated for relapsed or refractory adult large B-cell lymphoma, with its associated side effects including cytokine release syndrome (CRS) and neurotoxicity [38]. Although CAR-T therapy has been formally applied to leukemia and lymphoma, which typically have limited tumor-specific molecules, it's important to address issues related to immune evasion and T-cell depletion. Significant progress has been made in studying T-cell depletion, with a primary focus on controlling and inhibiting this process to effectively treat tumors and broaden the population benefiting from this therapy[39]. a. The absence of the TET2 protein can lead to the prolonged maintenance of T cells in the central memory state, thereby preventing target cell evasion, increasing the population of memory T cells, enhancing perforin and granzyme levels, and ultimately improving the efficacy of CAR-T therapy. Moreover, intervention with drugs or gene-editing technologies to restore TET2 protein expression or function can not only enhance the effectiveness of CAR-T therapy but also potentially reduce treatment costs [40]. b. Nr4a transcription factors are prominently expressed in CD8+ T cells during chronic viral infections and in cancer. Interestingly, the absence of Nr4a expression can markedly enhance the efficacy of CAR-T therapy. Animal studies have demonstrated that mice lacking Nr4a expression in CAR T cells exhibit substantially reduced tumor growth and prolonged survival. Therefore, inhibiting the expression of Nr4a transcription factors represents a promising strategy to counteract T-cell depletion and improve the effectiveness of CAR-T therapy in the future [41]. c. Decitabine, an epigenetic drug, operates by inhibiting DNA methylation. It has a specific impact on depleted T-cells that are linked with epigenetic alterations. By targeting these cells, decitabine facilitates their transformation into long-lasting functional memory T-cells. This intervention also helps alleviate the hindrance that depleted T-cells pose in immune system regulation against infections and tumors. Furthermore, decitabine usage may restrict the efficacy of immunosuppressants [42]. Moreover, PD-1/PD-L1 immune checkpoint inhibitors have shown significant efficacy in controlling tumor growth [43]. This approach is anticipated to be effective in treating a wide range of cancers.

3.3 Tcr-Transduced T Cells

TCR-transduced T cells are typically produced by genetically inducing tumor-specific TCR expression. This process commonly involves cloning the specific

antigen-targeting TCR into a retroviral vector. Patient blood samples are collected, and peripheral blood mononuclear cells (PBMCs) are isolated. These PBMCs are then stimulated with CD3 in the presence of IL-2 and subsequently transduced with the retrovirus containing the antigen-specific TCR. The transduced PBMCs are further expanded in vitro before being reintroduced into the patients through infusion. [44]. TCR-transduced T cells offer numerous advantages and solutions compared to other immunotherapies. Primarily, they possess a robust capability to be generated against a wide array of tumor antigens [45]. Secondly, engineering strategies such as the incorporation of disulfide bonds and optimization of TCR genes enable straightforward enhancement of modified TCR expression [46]. Finally, TCR-transduced T cells have the ability to bypass self-tolerance to specific self-antigens and exhibit long-term persistence in vivo [47]. Although TCR-transduced T cells offer versatility and robustness, a major challenge arises from the potential unintended pairing of transferred TCR chains with endogenous TCR chains. This can lead to the formation of mispaired dimers, resulting in decreased reactivity [48]. To address these challenges, a study employed modern CRISPR-mediated gene editing techniques to knockout endogenous TCR chains. This approach aimed to enhance surface expression of the modified TCR. The study demonstrated that CD4 and CD8+ T cells redirected more effectively against patient-derived B acute lymphoblastic leukemia compared to standard TCR transfer. This resulted in a stronger response and increased sensitivity towards the tumor antigen [49]. One tumor antigen of significant interest is NY-ESO-1, classified as a cancer germline antigen. It is expressed in approximately 70–80% of synovial cell sarcoma cases and 25% of melanoma patients. In a pilot trial, autologous peripheral blood mononuclear cells (PBMCs) were retrovirally transduced with NY-ESO-1-specific TCR and then infused into patients with metastatic melanomas and metastatic synovial cell sarcomas. Results from the trial showed that 11 out of 18 patients with synovial cell sarcoma and 11 out of 20 patients with melanoma exhibited an objective clinical response [50].Cyclophosphamide may use against colorectal cancer [51].

4. Monoclonal Antibodies Therapy

The efficacy of monoclonal antibodies (mAbs) as therapeutic agents relies on three key features: (i) The Fc moiety, which facilitates antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC). (ii) The Fab moiety, which ensures high specificity and affinity for antigen binding. (iii) A molecular mass of approximately 150 kDa, extending the circulatory half-life of the mAb up to 21 days. The mechanism of tumor cell destruction by mAbs involves: (i) Binding to specific receptors on tumor cells via the Fab portion of the antibody, triggering cytotoxicity through the Fc portion of the antibody, or (ii) Binding to specific receptors on tumor cells via the Fab portion of the antibody, thereby blocking important signaling pathways via the Fab portion of the antibody, or a combination of both mechanisms. Over the past 15 years, antibody-based immunotherapy has emerged as a successful strategy for treating patients with hematological malignancies and certain solid tumors. To enhance effector functions, mAbs have been conjugated to various entities such as radioisotopes, chemotherapeutic agents, bacterial toxins, cytokines, and enzymes [52]; thereforemAbs are classified as follows:

4.1 Naked Mabs

These monoclonal antibodies (mAbs), devoid of drug or radioactive attachments, target specific molecules or antigens present on tumor cells. They can act by blocking crucial signaling pathways, such as EGFR, or by facilitating the immune system's destruction of tumor cells through mechanisms like antibody-dependent cellular cytotoxicity (ADCC), or a combination of both [52].ADCC, or antibody-dependent cellular cytotoxicity, is a significant mechanism for killing tumor cells, facilitated by the interaction between the Fc region of an antibody and FcγRIIIareceptors found on the surface of immune cells. Monoclonal antibodies (mAbs) can bind to specific targets on the cell surface via their Fab region and then engage effector cells expressing FcγRIIIa using the Fc region of the mAb. This interaction ultimately leads to the killing of the tumor cell. ADCC is considered a crucial mechanism of action for FDA-approved mAbs such as rituximab and trastuzumab [53].Rituximab, a chimeric monoclonal antibody (mAb) targeting the B-cell surface antigen CD20, holds the distinction of being the first mAb approved by the FDA for therapeutic use against B-cell non-Hodgkin lymphoma (NHL), CD20-positive NHL, and chronic lymphocytic leukemia (CLL) [54]. Trastuzumab, commonly known as Herceptin, is another mAb directed against human epidermal growth factor receptor 2 (HER2 or HER2/neu), a tyrosine kinase membrane receptor. This receptor is overexpressed on approximately 30% of breast cancer cells in a subset

of breast cancer patients. Trastuzumab monotherapy has shown efficacy in achieving prolonged disease stability in a significant number of patients with advanced-metastatic breast cancer [55].Several monoclonal antibodies (mAbs) approved by the FDA have demonstrated success in treating patients with solid tumors: bevacizumab targeting vascular endothelial growth factor (VEGF) (as first-line and second-line treatment of metastatic colon cancer in combination with 5-FU chemotherapy; in combination with carboplatin and paclitaxel chemotherapy as first-line treatment of advanced NSCLC patients who have not yet been treated with chemotherapy; as a single agent in patients with glioblastoma whose tumors have progressed after treatment; and for treating mRCC patients in combination with IFN-α); cetuximab targeting EGFR (as a single agent in HNSCC patients with failure to platinum-based therapy; in combination with radiotherapy for regionally advanced HNSCC; and as palliative treatment of pretreated metastatic EGFR-positive colorectal cancer); panitumumab targeting EGFR (as a single agent for treating pretreated EGFR-positive metastatic colorectal cancer); alemtuzumab targeting CD52 (as a single agent for treating CLL); and ofatumumab targeting CD20 (for the treatment of CLL patients refractory to fludarabine and alemtuzumab) [56-60].

4.2 Conjugated/Tagged/Labeled/Loaded mAbs

Indeed, these monoclonal antibodies (mAbs) are designed to target specific molecules or antigens expressed on tumors. When coupled with a cytotoxic or radioactive agent, they enable the delivery of a toxic substance directly to the tumor site. This approach is often referred to as radioimmunotherapy (RIT) [61]. Ibritumomab tiuxetan is a radiolabeled monoclonal antibody (mAb) targeting the CD20 antigen expressed on B lymphocytes. It is FDA-approved for the treatment of various lymphomas. A randomized phase III trial comparing ibritumomab tiuxetan to rituximab in patients with relapsed or refractory non-Hodgkin lymphoma (NHL) revealed a higher overall response rate (80% versus 56%) and complete response (CR) rate (30% versus 16%) for ibritumomab tiuxetan. However, the time to disease progression was similar for both treatment groups [62].Brentuximab vedotin (Zevalin) represents an alternative approach utilizing mAbs coupled to chemotherapeutic agents, known as antibody-drug conjugates (ADC). In this case, brentuximab vedotin is a mAb conjugated to a chemotoxic drug called monomethyl auristatin E (MMAE), targeting the cell membrane antigen CD30 on lymphocytes. In a phase II clinical study (NCT00848926; ClinicalTrials.gov) involving patients with refractory Hodgkin lymphoma, brentuximab vedotin demonstrated significant efficacy, with complete remission observed in 34% of patients, partial remission in 40% of patients, and tumor regression in 94% of patients [63]. Brentuximab vedotin is indeed FDA approved for the treatment of Hodgkin lymphoma and anaplastic large-cell lymphoma. Trastuzumab emtansine (T-DM1) is another example of an antibody-drug conjugate. It is FDA approved specifically for the treatment of HER2-positive breast cancer [64].

4.3 Bispecific Monoclonal Antibodies

The described mAbs are termed bispecific antibodies, formed by coupling two different mAbs together. This construct allows the mAb to bind to two separate proteins simultaneously, directing the immune system to act against the tumor. Blinatumomab is a notable example, where one part of the mAb binds to the CD19 protein expressed on B-lineage acute lymphoblastic leukemia cells, while the second part of the mAb binds to the CD3 protein found on T cells. This linkage activates the T cells, enabling them to exert cytotoxicity on the CD19+ tumor cells. Blinatumomab received FDA approval in 2014 based on the results of a phase II trial in patients with relapsed or refractory acute lymphoblastic leukemia. In this trial, 40% of patients achieved a complete response (CR) or complete response with partial hematologic recovery (CRh) [65].

5. Cancer Vaccines

Cancer vaccines are categorized into two types: Prophylactic vaccines and Therapeutic cancer vaccines. Prophylactic vaccines aim to prevent primary and secondary cancers, thereby reducing cancer rates, illness, and fatalities. These vaccines are engineered to stimulate the immune system's recognition and targeting of specific viruses before they can lead to infection. They are typically administered to individuals who are in good health [66]. The U.S. FDA has approved two prophylactic vaccines. One targets the hepatitis B virus, which is linked to hepatocellular carcinoma, a form of liver cancer. The other vaccine, Gardasil, addresses human papillomavirus (HPV), which is associated with approximately 70% of cervical cancer cases [67].Therapeutic cancer vaccines are administered to cancer patients with the aim of enhancing their immune

responses to eradicate cancer cells. These vaccines can be classified into several major categories based on their content, including cell vaccines (tumor or immune cell), protein/peptide vaccines, and genetic (DNA, RNA) vaccines. Two examples of therapeutic cancer vaccines are Bacillus Calmette–Guérin (BCG) and sipuleucel-T (Provenge®). BCG vaccine is approved for patients with early-stage bladder cancer, while sipuleucel-T (Provenge®) is approved for asymptomatic metastatic castrate-resistant prostate cancer. Sipuleucel-T works by stimulating an immune response against the prostatic acid phosphatase antigen, which is commonly overexpressed in prostate cancers [68,69].

6. Cytokines Therapy

Cytokines serve as molecular messengers facilitating communication among immune system cells, enabling them to mount a coordinated, robust, yet self-limited response to a specific antigen. These proteins, whether secreted or membrane-bound, act as mediators of intercellular signaling, thereby regulating the immune system's homeostasis. Produced by both innate and adaptive immune cells, cytokines are elicited in response to microbial pathogens as well as tumor antigens [70]. Two cytokines that are currently approved by the FDA for clinical use are interferon alpha (IFN-α) and interleukin-2 (IL-2).

6.1 Interferon α

When administered subcutaneously in renal cell carcinoma, these cytokines have demonstrated tumor regression. Additionally, they have exhibited promising outcomes in stage 3 melanoma. However, the combination of IFN-α and IL-2 has been associated with partial responses and increased toxicity. IFN-α serves various roles in tumor control, such as directly eliminating tumor cells by inducing senescence and apoptosis. It also enhances effective antitumor immune responses by promoting dendritic cell (DC) maturation and augmenting T-cell cytotoxicity [71]. Intron-A use against melanoma, renal and kidney cancer, Hairy cell leukemia, CML, Kaposi's sarcoma [72].

6.2 Interleukin-2

This cytokine is approved by the US FDA for metastatic melanoma treatment. These cytokines elevate the levels of natural killer (NK) cells and tumor-infiltrating lymphocytes (TILs) within the lesion. Administration of IL-2 in the perilymphatic region has been shown to enhance the survival rate of patients with head and neck squamous cell carcinoma (HNSCC). Moreover, patients who received monoclonal antibody (MoAb) therapy after surgery demonstrated increased levels of tumor-reactive T cells [73]. Proleukin (aldesleukin) use against renal and kidney cancer, melanoma, lymphoma [72].

Table1. *Summery of different immunotherapy on cancer.*

Immunotherapy	Agent	Indication
Immune Checkpoint Therapy		
Anti-CTLA-4 Therapy	Ipilimumab	Melanoma, renal cell carcinoma (RCC), prostate cancer, urothelial carcinoma, and ovarian cancer
Anti-PD-1/PD-L1 Therapy	Nivolumab	Metastatic melanoma, non–small-cell lung carcinoma (NSCLC), metastatic RCC, and classical Hodgkinlymphoma
LAG-3 or CD223	Immuntep (IMP321), Relatlimab (BMS-986016)	Melanoma, prostate cancer, metastatic breast cancer and solid tumors
TIM-3	MBG453	Advanced malignancies
Adoptive Cell Therapy		
TILs		Melanoma, pancreatic cancers, colorectal cancers
CAR-T	Novartis's tisagenlecleucel-T (Kymriah).	Recurrent or refractory B-cell acute lymphoblastic leukemia.
	Kite/Gilead's axicabageneciloleucel (Yescarta).	Refractory adult large B-cell lymphoma.
TCR-Transduced T Cells	Cyclophosphamide	Colorectal Cancer

Monoclonal Antibodies Therapy		
Naked mAbs	Rituximab	B-cell non-Hodgkin lymphoma (NHL), CD20-positive NHL, chronic lymphocytic leukemia (CLL).
	Trastuzumab (Herceptin)	Breast cancer.
	Bevacizumab	Solid tumors.
	Cetuximab	HNSCC patients.
	Panitumumab	Metastatic colorectal cancer.
	Alemtuzumab, Ofatumumab	CLL.
Conjugated/Tagged/Labeled/Loaded mAbs	Ibritumomab tiuxetan, Brentuximab vedotin	Different lymphomas.
	Trastuzumab emtansine (T-DM1)	HER2-positive breast cancer.
Bispecific Monoclonal Antibodies	Blinatumomab	Relapsed or refractory acute lymphoblastic leukemia
CANCER VACCINES		
Prophylactic vaccines	Gardasil	Cervical cancer
Therapeutic cancer vaccines	Bacillus Calmette–Guérin (BCG)	Early-stage bladder cancer.
	sipuleucel-T (Provenge®)	Prostate cancers
CYTOKINES THERAPY		
Interferon α	Intron-A	Melanoma, renal and kidney cancer, Hairy cell leukemia, CML, Kaposi's sarcoma
Interleukin-2	Proleukin (aldesleukin)	Renal and kidney cancer, melanoma, lymphoma

7. Conclusions and Future Perspectives

Nowadays, anti-tumor immunotherapy is increasingly pivotal in cancer treatment. Promising results have emerged from trials targeting various malignant tumors. Enhanced efficacy and reduced adverse reactions are achieved through novel targets and methods like combination therapy. However, controversies persist, including treatment unpredictability, empirical approaches, individual cases with severe adverse reactions, and high treatment costs. Recognizing the dynamic and complex nature of tumor development, personalized immunotherapy tailored to tumor characteristics and individual immune status is crucial for optimal outcomes. Immunotherapy represents a significant breakthrough in cancer treatment, with a focus on restoring specific immune pathways in anti-tumor processes. Identifying suitable targets and refining treatment strategies to mitigate toxicity and side effects are essential for addressing challenges such as postoperative recurrence and metastasis. While the path of immunotherapy presents substantial challenges, it also offers significant opportunities for advancement and maturation in the future.

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