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THE REVIEW ON IMMUNOTHERAPY IN CANCER TREATMENT: CURRENT ADVANCES AND FUTURE DIRECTIONS

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ABSTRACT

One disease that arises from unchecked cell growth and proliferation is cancer. Many cancer types now have lower death rates as a result of early diagnosis techniques. Still, cancer is the second leading cause of mortality globally, after cardiovascular illnesses. Consequently, the major goal of cancer research has been to provide more potent therapies in order to lower the number of cancer-related deaths. Acquiring a deeper comprehension of the molecular pathways within cancer cells has led to changes and evolutions in the treatment of cancer. Developing therapy modalities with the highest response rate and the fewest adverse effects is the top objective for research. In this regard, immunotherapies have ushered in a new phase of cancer therapy. The future of next-generation therapeutic approaches is summarized in this article by presenting the most popular immunotherapy techniques.

According to recent research, biological therapies that target the tumor microenvironment specifically may engage the immune system. Clinical trials have demonstrated significant progress in the use of immune cells—particularly T cells, which are essential for cell-mediated immunity—for the treatment of malignant tumors. As a result, the treatment of cancer through therapeutic approaches and developmental strategies is the main subject of this article. The immunomodulatory response, the role of important tumor-infiltrating cells, the molecular elements, and prognostic biomarkers are highlighted in this review. Recent developments in treatment approaches are also covered.

KEYWORDS: *Cancer, immunotherapy, CAR-T-cell therapy, monoclonal antibody, mRNA vaccine, tumor microenvironment, combination therapy, checkpoint-inhibitors.*

INTRODUCTION

Cancer is a disease of unchecked cell proliferation. Certain characteristics set cancer cells apart from healthy ones: they continue to express proliferative signals, are immune-evading, resistant to cell death, insensitive to signals that suppress growth, have an infinite capacity for replication, encourage angiogenesis, promote invasion and metastasis, and rewire cellular and environmental metabolism(1). Cancer cells escape from apoptosis(2) and are not captured by cell cycle regulatory mechanisms as a result of their genetic abnormalities. Genetic changes and environmental variables have a crucial influence in the development of cancer. These include chemical carcinogens like alcohol intake, smoking, and asbestos exposure; physical carcinogens like ionizing and UV radiation; and food consumption of aflatoxin and arsenic. Biological carcinogens, such as infections from specific bacteria, viruses, or parasites, are responsible for one-third of cancer deaths. Other factors that contribute to cancer mortality include smoking, alcohol usage, having a high body mass index, eating an unhealthy diet, and not getting enough exercise(3, 4).

While many cancer types now have lower death rates because to good treatment options, the majority of cancer research is concentrated on creating more potent medicines to lower the death toll. A deeper comprehension of the molecular pathways behind cancer has led to changes and evolutions in cancer treatment. Globally, there are more and more cancer patients, which presents serious issues. But the hunt for the medication that has the best response rate and the fewest adverse effects is still going strong(5). Treatments for cancer that are employed in the clinic include surgery, hormone therapy, photodynamic therapy, targeted therapy, radiotherapy, chemotherapy, stem cell transplantation, and immunotherapy(6). Due to the resistance mechanisms these therapies have against cancer, they are frequently used in combination.

This paper discusses the elements that might be useful in establishing national and international roadmaps and forecasts the future of next-generation cancer therapies based on existing research.

IMMUNOTHERAPIES

A sophisticated approach to treating a variety of cancers, including solid and hematological tumors, immunotherapy has emerged as one of the available therapeutic alternatives.

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Immunotherapies aim to combat cancer by using the patient's own immune system, opening the door to more specialized and potent treatments. For patients with various malignancies, cancer immunotherapy is a viable treatment option because it has comparatively fewer side effects than chemotherapy[7]. Monoclonal antibodies (mAbs), mRNA vaccines, immune checkpoint inhibitors, and adoptive cell transfer in the form of chimeric antigen receptor (CAR)-T cell therapies are among the immunotherapy medications available today (Fig 1)[8].

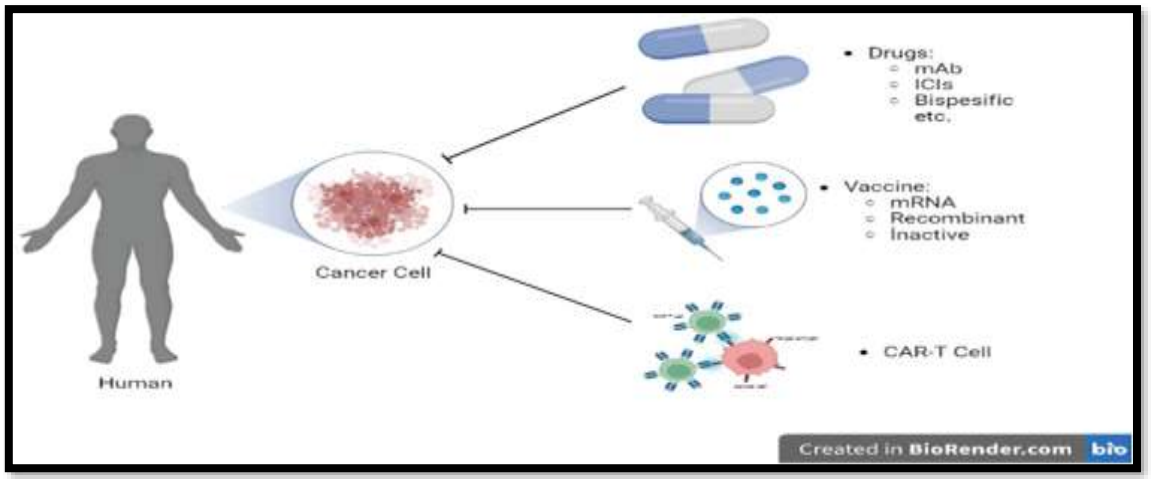

Fig. 1: Current advances and future prospects in cancer immunotherapies.

Depending on the immune response, cancer immunotherapy is categorized as either active or passive. Agents such as lymphocytes, cytokines, or mAbs that boost the body's natural anti-tumor response are used in passive immunotherapy. Vaccination, non-specific immunomodulation, and immune system activation by selective antigen receptor targeting to tumor cells are examples of active immunotherapy techniques[9]. T-cell immune checkpoint pathways are mostly linked to immune response resistance mechanisms. Therefore, reducing immune response evasion can be achieved by examining novel immunological checkpoints and molecular pathways. Finding tactics that will improve T-cell continuity and proliferation, decrease immunosuppression, and stop T-cell depletion is essential to improving the response to immunotherapeutics[10].

MONOCLONAL ANTIBODIES (mAbs) FOR CANCER THERAPY

mAbs are proteins that attach to a particular molecular target and are either synthesized or generated by B lymphocytes[8]. Humanized monoclonal antibodies have been designed targeting relevant targets to achieve anti-cancer effects in preclinical models and patient studies[11]. Because mAbs are significantly more selective and have fewer cytotoxic effects, they have recently become a highly favored cancer therapeutic[12].

Research has indicated that mAbs[13] may enhance cancer patients' overall survival. Based on these investigations, numerous anti-cancer mechanisms, including complement-dependent cytotoxicity (CDC), antibody-dependent cell-mediated cytotoxicity (ADCC), apoptosis promotion, and cell proliferation inhibition, have been linked to recovery[14]. Production within the purview of this technology is carried out employing immortal cancer B-cell myeloma cells and immunized mouse spleen cells capable of producing antibodies[15]. For oncological illnesses, the US Food and Drug Administration (FDA) has approved more than 22 immunotherapeutic medications; a few of these are included in Table 1.

Name	Target	Cancer (Year of First Approval)
Adagrasib	RAS GTPase family	Non small cell lung cancer (2002)
Bevacizumab	VEGF	Colorectal ,lung ,cervical, renal cell cancers.
Cemiplimab	PD-1	Cutaneous squamous -cell carcinoma (2018)
Durvalumab	PD-L1	Bladder cancer (2017)
Elacestrant	ER,HER2	Breast cancer (2023)
Teclistamsab-cqyv	CD-3	Multiple myeloma(2022)

Table 1: FDA-Approved Immunotherapeutic Drugs for Different Cancer Types.

IMMUNE CHECKPOINT INHIBITORS

Immunocheckpoint inhibitors (ICIs), which have recently been developed, have changed the treatment of cancer and increased patient lifespan. The therapy of many cancer forms, such as non-small cell lung cancer (NSCLC), melanoma, head and neck cancer, bladder cancer, and renal cell carcinoma, has been authorized for immune checkpoint inhibitors (ICIs) that target checkpoint proteins

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like CTLA-4 or PD-1.[16] Immune cells have "checkpoint" proteins that function as on/off switches to regulate immune responses. Checkpoint inhibitors prevent T cells from destroying tumor cells, which aids the immune system in its indirect attack on cancer cells.[17] By connecting to a programmed death ligand 1 (PD-L1) cell, T cells with PD-1 expression function as a kind of "off switch" that prevents T cells from attacking other cells in the body. T cells are instructed to leave the other cell alone when PD-1 binds to PD-L1. However, certain cancer cells express a lot of PD-L1 in order to evade the immune response.PD-1 and PD-L1 checkpoint inhibitors are the main immunotherapies used to treat advanced lung cancer, according to numerous studies conducted on a range of tumor types .

A variety of human malignancies have shown therapeutic benefit when treated with clinically licensed antibodies against PD-L1/PD-1 . Accordingly, increased tumor metastasis, improved drug efflux via multidrug resistance protein 1 (MDR-1), and activation of PD-L1 expression severely impede cis-platinum (Cis-Pt)-mediated treatment. Metformin-modified chitosan (Ch-Met) can accumulate selectively in mitochondria and cause disruptions to mitochondrial activity, ultimately leading to decreased tumor metastasis and inhibition of PD-L1 expression. Consequently, it was shown that Ch-Met could sensitize Cis-Pt's chemotherapeutic efficacy . Consequently, a variety of cancer types are being treated with antagonistic antibodies-mediated immunotherapeutic approaches that target PD-1 or its ligand, PD-L1, and can considerably increase patient survival. Therefore, certain small-molecule inhibitors are being developed, evaluated, and authorized in order to block the expression and/or activity of PD-L1 [109,112,113]. Table 2 presents a summary of small-molecule inhibitors that may block the processes governing PD-L1 expression.

Target	Drug	Cancer type	Modulated PD1
Histone methyltransferase EZH2	Tazemetostat and DZNep	Prostate cancer	Transcriptional upregulation of PD-L1
	Tazemetostat (Tazverik)	Epithelioid sarcoma (2020)	Transcriptional upregulation of PD-L1 via decreased H3K27me3, FDA approved
Histone deacetylase inhibitor	Vorinostat (Zolinza)	Cutaneous T cell lymphoma (2006)	Transcriptional upregulation of PD-L1, FDA approved
DNA methyltransferases	Decitabine (Dacogen)	Myelodysplastic syndrome (2006)	Transcriptional upregulation of PD-L1 via decreased DNA methylation in the PD-L1 promoter region, FDA approved
ZFP36 (Tristetraprolin)	Doxorubicin	NSCLC and breast cancers	Downregulates translation of PD-L1

Table 2: Small drugs with checkpoint inhibition capacity in cancer immunotherapy.

PERSONALIZED RECOMBINANT CANCER VACCINES

Cancer immunotherapy becomes a crucial component of the cancer treatment plan by concentrating on TAAs. It provides a number of therapeutic advantages and doesn't have any unanticipated side effects.

These developments therefore necessitate the creation of recombinant vaccines for cancer immunotherapy that are both extremely effective and less toxic. Remarkably, the number of mutations among tumor types is significant, with 10 s to 1000 s mutations . Greater immunogenicity and survival following checkpoint blockade treatments have been linked to higher mutational events in the tumor. For example, treatment with ipilimumab and tremelimumab, antibodies against cytotoxic T-lymphocyte antigen 4 (CTLA-4) has been shown to prolong overall survival in patients with melanoma . It's interesting to note that very few gene variations that express TAA-specific peptides spontaneously elicit an immunological response . Selective binding to MHC class II, which implies the function of CD4+ T cells rather than CD8+ T cells, is necessary for TAA-induced cytokine responses .Nonetheless, numerous investigations have exhibited the significance of CD4+ and CD8+ T cell reactions to TAA vaccinations in diverse forms of malignancy. Prediction algorithms are used to determine whether tumor-derived peptides may combine with the patient's MHC alleles to generate an acceptable TAA. [18]However, more investigation and technology advancements to comprehend the processes of antitumoral immune responses could lead to increased accuracy and efficacy. Numerous advancements in immunotherapeutic strategies are required to solve this issue.

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TUMOR MICROENVIRONMENT IN CANCER

Tumor microenvironment, or TME, has a vital role in the formation and progression of cancer, influencing the growth and metastasis of a tumor. The microenvironment of cancer cells is made up of blood arteries, immunosuppressive cells, and an abundance of fibrous matrix. These interactions allow the tumor tissue to be shielded from the immune system's grasp (Figure 1). The growth and spread of cancer cells are dependent on this interaction because it promotes the heterogeneity of cancer cells, clonal evolution, and increased multidrug resistance. Their clinicopathologic importance in predicting outcomes and therapeutic success has been clarified in a number of papers · Numerous investigations have demonstrated that the course of tumor growth is determined by a dynamic and mutualistic interaction between the surrounding stroma and tumor cells. It is commonly known that tumor-related structures and activated signaling pathways play a significant role in cancer cells and the tumor microenvironment. Patients with cancer have been found to have differences in the compositions of resident cell types within the TME, such as mesenchymal stem cells, resting fibroblasts, dendritic cells (DCs), cytotoxic T cells (CD8+T), helper T cells (CD4+T), tumor-associated macrophages (TAMs), and associated inflammatory pathways . TAMs are essential for the growth of tumors because they induce genetic instability, facilitate metastasis, nurture cancer stem cells, and suppress protective adaptive immunity. Typically, they express surface molecules that are distinctive of them, like the macrophage mannose receptor 1 (CD206) and the hemoglobin scavenger receptor (CD163) .

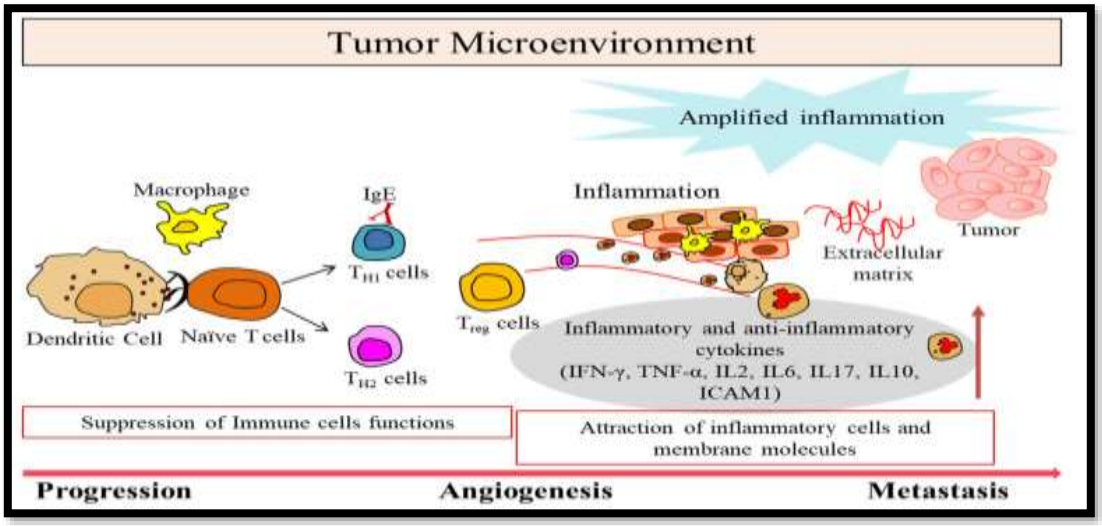

Fig.2: Tumor microenvironment in cancer. Schematic depicting progress of tumor involving suppression of immune function, tumor cells proliferation leading to metastasis.

CAR-T-CELL THERAPY

In CAR-T-cell therapy, autologous T-cells from patients are used to create a tumor antigen-specific CAR ex vivo, which is then injected back into the patient. More recent research has shown that leukemia regression may be induced in vivo by using nanocarriers containing CAR genes and gene editing instruments. At the moment, early phase investigations on B-cell malignancies comprise the majority of clinical trials employing CAR-T cells. The most often used target is CD19, which has been used more recently together with other antigen targets but mostly alone.[19]

Particularly in the case of B-cell acute lymphoblastic leukemia, CAR-T-cell treatment has demonstrated promising clinical outcomes. However, because of tumor histological characteristics, the absence of antigens specific to the tumor, the immunosuppressive tumor microenvironment, and possibly fatal tumor toxicity, its effects are restricted in solid tumors[43]. Scientists are working to get beyond some of these obstacles, though, especially by creating CAR-T agents. Alongside obstacles, encouraging outcomes will continue to emerge as research into CAR-T treatments continues.

CONCLUSION

Cancer immunotherapy is a way to use the body's immune system to combat cancer. It may be possible to modify the immune system to eradicate cancer by appropriately initiating the immune responses without causing unintended effects. Not just T cells, but also other immune cells including natural killer cells and antigen-presenting cells, can be involved in this. New optimism has emerged in the fight against cancer as a result of the effectiveness of immunotherapies and cancer vaccines in clinical studies. Despite having more immune-related side effects, these tactics are more tolerable than conventional chemotherapeutic drugs. Our confidence in treating cancer has increased with the development of novel biological therapy techniques. Clinical decision support systems powered by artificial intelligence may offer a quick fix for this issue in the near future.[20]

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