CANCER IMMUNOTHERAPY –A PROPITIOUS GENESIS IN CANCER INDAGATION

Abstract

One of the most important developments in oncology in recent years is cancer immunotherapy. After decades of unsatisfactory results, immunotherapy has finally turned the tide and is now a clinically proven treatment for many malignancies. Various Immune therapies denote astonishing favorable outcomes over the decades and have been acquiesce for the treatment of various cancer therapies.While the recent development of immunotherapy with checkpoint inhibitors has drastically altered the approach to treating various cancers due to the significant survival advantages. However patient reactions towards immunotherapies are varying and around 50% of cases are obstinate to these agents. Additionally, immunotherapy develops become a busy area of study in both the oncology and cancer biology fields. This article makes conceptual and historical review which summarizes the main advances in our understanding of the role of the immune system in cancer immunotherapy and emerging data for the treatment of triple negative breast cancer, gastric cancer, hepatobiliary cancer, while describing the methodological details that have been successfully implemented in cancer treatments and that may hold the key to improve therapeutic approaches .Furthermore the current development in nanotechnology based cancer immunotherapy have been presented and discussed.

Keywords: Cancer immunotherapy triple negative breast cancer, gastric cancer, hepatobiliary cancer, nanotechnology.

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I. INTRODUCTION

In the late 19th century, William B. Coley, commonly known as the "Father of Immunotherapy," proposed the idea of using the immune system's capacity to fight cancer. In 1891, Coley's trials involved the live injection of lS. pyogenes and S. marcescens bacteria into cancer victims who were unable to undergo surgery produced encouraging results [3,4,5]. Following this, Thomas and Macfarlane's approach of the "cancer immune surveillance" conjecture and Paul Ehrlich's 1909 theory that the transformed cells are eliminated by the immune system impute the basis for the perception of cancer immunology[6]. A new standard in cancer treatment has emerged as a result of our growing understanding of immune surveillance. In addition to influencing tumor immunogenicity, the immune cells engage in a binary role in preventing tumor development by triggering the innate and adaptive immune systems [7]. Since the past few decades, there has been an advancement in understanding of how the immune system is affected by cancers , which has led to the invention of ground-breaking therapies that cease the immune tumor evasion. It was Allison and Honjo's findings of the immune checkpoints of T-cell CTLA-4 and PD-1 that launched the study of immunology of cancer into the current epoch of cancer immunotherapy and made them the recipient of the Nobel Prize in Physiology or Medicine in 2018[8]. Despite advances in the development of anticancer medications and treatments, cancer still has the greatest fatality rate due to its dismal prognosis. Examples of conventional cancer therapies include chemotherapy, radiation therapy, and targeted therapy. The limitations of conventional medicines include lack of selectivity, non-specific cytotoxicity, inadequate drug delivery to cancer locations, and multidrug resistance, all of which result in less effective/efficient therapeutic outcomes.

Recent decades have seen a rise in the acceptance of cancer immunotherapy as a promising treatment alternative for cancer patients, with promising clinical results. Due to monoclonal antibodies' outstanding results as immune checkpoint inhibitors in preclinical and clinical studies and the Food & Drug Administration's (FDA) subsequent approval of these molecules for cancer therapy, the landscape of cancer treatment has changed. However, due to the short circulation duration of immune checkpoint inhibitors and shorter effect times, only a tiny proportion of patients and indications have benefited from the majority of cancer immunotherapies [1]. Both the field of oncology and the study of cancer biology are now actively researching immunotherapy. This review critiques preclinical studies and clinical trial outcomes from immune molecule based-therapies, oncolytic virus based therapies, immune checkpoint inhibitors, adopted cell therapies,and vaccine therapies.

II. IMMUNOTHERAPY FOR TRIPLE-NEGATIVE BREAST CANCER: DEVELOPMENT AND FUTURE PROSPECTS

Breast cancers have been categorized into four main molecular subtypes based on the immunohistochemistry (IHC) expression of traditional hormone and growth factor receptors such as the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2).Worldwide, breast cancer continues to be the most common cancer in women. In the United States, it is anticipated that there will be 43,600 fatalities and around 281,550 new cases in 2021. The 2013 St. Gallen International Breast Cancer Conference proposed a revised definition of breast cancer molecular subtypes: IHC staining results for patient samples were used to calculate the percentages for luminal A (ER/PR+, HER2, Ki67+

20%), luminal B (ER/PR+ 20%, HER2, Ki67+ 20%), HER2+ B2 (ER/PR+, HER2 overexpression), HER2 overexpression (ER, PR, HER2 overexpression), basal-like triple-negative breast cancer (TNBC,ER−, PR−, and HER2−), and other subtypes[10]. Selective estrogen receptor modulators, aromatase inhibitors, and ER degraders are available as treatments for patients with luminal A or luminal B subtypes of breast cancer. Treatment options for patients with HER2 overexpression include tyrosine kinase inhibitors, antibody-drug conjugates, and monoclonal antibodies (mAbs) that specifically target HER2. a significant subset of the fourth breast cancer.

Although most breast cancer patients do not respond well to immunotherapy, a subset of TNBC has been shown to have high tumor mutation burden (TMB) and high tumor-infiltrating lymphocytes (TILs), resembling the features seen on melanoma or lung cancers that can benefit from the treatment of ICIs. As an outcome, the discovery of TNBC-targeting immunotherapies is being made feasible by severe sickness; immunogenicity. With the FDA's recent approval of atezolizumab alongside with the chemotherapeutic drugs nab-paclitaxel for the treatment of PD-L1-positive unresectable, locally developed, or metastatic TNBC, a new era of immunotherapy for TNBC has begun. The Impassion130 clinical trial's favorable outcomes, which suggested that patients receiving atezolizumab/nab-paclitaxel treatment for PD-L1-positive TNBC had median overall survival (OS) that was nearly 10 months longer than those receiving placebo/nab-paclitaxel treatment, laid the bedrock for the combination therapy's final market approval.

1. Immune Molecule Based Breast Cancer Therapy

- **Cytokine:** Cytokines are vital immune system regulators of the innate and adaptive immune systems that control the proliferation, differentiation, survival, and effector functions of leukocytes through communication over short distances in a paracrine and autocrine fashion. They possess the potential to boost the immune response against tumors. Since the discovery of interleukin-1 (IL-1) as an endogenous pyrogen " in 1953[9], the use of exogenous cytokines for cancer treatment through stimulation of a patient's own immune system has been avidly examined in both scientific and clinical investigations.

  Two cytokines have recently gained the FDAs approval for use in cancer therapy [11]. As a single- agent cytokine therapy for cancer, interferon alpha 2 (IFN-) was initially given FDA approval in 1986. As a result of Rosenbergs seminal discovery revealing that injections with T-cell growth factor, later referred to as interleukin-2 (IL-2), can shrink tumors in humans, interleukin-2 (IL-2) was approved by the FDA as an immunotherapeutic cytokine monotherapy for the treatment of metastatic kidney cancer in 1991 and later for the treatment of metastatic melanoma in 1998. Both IL-15 and IL-21, members of the IL-2 family, are under scrutiny to determine if they have any prospective for cancer treatments [9]. In 1993, it came to light that the formidable cytokine GM-CSF accelerated the proliferation of myeloid cells. It is being evaluated as an adjuvant immunomodulator medication to stimulate anti-tumor immunity in both basic and clinical studies right now [12].Numerous approaches have been executed in the clinic to get around the issues associated with cytokine administration, including cytokines paired with checkpoint inhibitors, cytokines combined with anticancer mAbs to enhance the antibody-dependent

cellular cytotoxicity (ADCC) of these antibodies, and antibody-cytokine fusion proteins that stimulate tumor-specific immune responses. Oncolytic viruses are being used in combination therapy in clinical investigations with cytokines. Talimogene laherparepvec (T-VEC; ImlygicTM), an oncolytic herpes simplex virus that uses GM-CSF expression as an immune enhancer and was approved by the FDA for use in cancer immunotherapy in 2015, exemplifies how cytokines can enhance the oncolytic virus-induced immune response against tumors [9].

- **Immune Checkpoint Inhibitor:** An ICI can trigger the immune system, which is often suppressed by cells associated with tumors or the tumor milieu, to target cancer cells. The FDA's ratification to the anti-PD1 antibodies Keytruda (pembrolizumab), Opdivo (nivolumab), and ICI anti-CTLA-4 antibody Yervoy (ipilimumab) in 2014 and 2015 are the highlights of immunotherapy, heralding the start of a modern age of cancer treatment [13]. Further, the FDA approved Libtayo (cemiplimab), Tecentriq (atezolizumab), Bavencio (avelumab), and Imfinzi (durvalumab), all of which are anti-PD1 and anti-PD-L1 antibodies [9]. Due to the small TMB (about 1 mutation/Mb) of breast cancers in comparison to melanoma or other tumor cells associated with high TMB, immunotherapy is not expected to be beneficial for individuals with breast cancer in general. But it has been shown that a subpopulation of TNBC exhibits high TMB (>10 mutations/Mb) and high TILs, characteristics seen in melanoma or lung tumors that potentially benefit from ICI treatment. Due to this aggressive disease's immunogenicity, there is now a chance for the development of immunotherapies that target TNBC [13-15].

2. **Neoantigen Cancer Vaccines:** Neoantigen cancer vaccines can stimulate the immune system to respond to specific cells associated with tumor antigen, resulting in development as well as proliferation of T cells that can recognize tumor antigens and inhibit tumor growth. Many vaccines have been developed to increase immunity against breast cancer because it is immunogenic, especially the TNBC subtype [16]. The efficacy of vaccines associated with dendritic cells against HER2-positive mammary cancer demonstrates, immunization for different oncogenes can stop and delay the development of mammary cancer. Additionally, neoantigens function as efficient targets for interception due to their high immunogenicity [17]. mRNA vaccines are promising next-generation vaccines that have ushered in a new era in vaccination science with the recent licensing of two COVID-19 mRNA vaccines (mRNA-1273 and BNT162b2). The vaccines associated with mRNA for cancer immunotherapy are anticipated to vigorously develop due to their proven therapeutic effects in various trials against multiple aggressive solid tumors.

3. **Oncolytic Virus-Based Therapy:** Oncolytic viruses (OVs) are a new class of therapeutic agents that promote anti-tumor responses through a dual mechanism of action that is dependent on selective tumor cell killing and the induction of systemic anti-tumor immunity. OVs are selectively replication competent in cancer cells, having the ability to proliferate after inceptive administration, and vigorously escalate the cells of tumor. 2015 saw the FDA approve talimogene laherparepvec (Imlygic, OncoVEXGM-CSF, and T-VEC), a mutant HSV-1, as the pioneer oncolytic virus in the therapy of melanoma. Tumor cells can be selectively killed using oncolytic virotherapy. Additionally, an infection with an oncolytic virus results in the production of cell debris and antigens that boost the

immune system [18]. The tumor is prevented from eluding the immune system and results in an immune response by a number of procedures, comprising viral invasion, lysis of oncogenes, the synthesis of neoantigens, and the invigoration of cellular danger pathways. Other than T-VEC, a few OV candidates are now in the development stage. The recruitment of CD8+ T cells is crucial for boosting the effectiveness of immune checkpoint inhibitors, according to research by Niavarani and colleagues using vesicular stomatitis virus (VSV) in conjunction with to an anti-PD-1 ICIs as a beneficial regimen in clinical trials of TNBC [19]. A legitimate, double-stranded RNA reovirus OV known as Pelareorep (Reolysin) was developed from the Dearing serotype 3 strain. One breast cancer patient in a phase I clinical trial employing pelareorep showed a stable illness after six or more weeks, while seven of the 19 patients showed some signs of response to tumor activity. There are some active therapeutic models for the therapy of breast carcinoma using the adenovirus (Ad) serotypes 2 and 5, which, now being assessed as oncolytic adenoviruses. Furthermore, the conjunction treatments that combine OVs with ICI, OVs and CAR-T are also being developed to treat solid tumors like TNBC [20].

III. IMMUNOTHERAPY FOR ADVANCED GASTRIC CANCER

The third most prevalent reason for cancer-related death is gastric cancer [21]. Patients with advanced stomach cancer have a dismal prognosis and a short lifespan of about one year due to the delayed diagnosis and lack of efficient therapy [22]. Radiotherapy, chemotherapy, and targeted therapy are the treatments that are most frequently utilized for advanced stomach cancer. Advanced gastric cancer is frequently treated with medications including imatinib, larotrectinib, entrectinib, and regorafenib [23,24]. However, the efficacy of these conventional treatments has been significantly constrained bymulti-drug resistance and tumor relapse.

The most frequently used immunotherapies for advanced gastric cancer include chimeric antigen receptor (CAR) T treatment, adoptive cell therapy, cancer vaccines, vascular endothelial growth factor A(VEGFA) antibodies, and immune checkpoint inhibitors (ICIs) . According to studies, ICIs such anti-PD-1/PD-L1 antibodies can successfully kill cancer cells by triggering the immune system. For cancer patients, ICI clinical trials have shown efficacy and safety. It should be noted that a number of ICIs,including pembrolizumab, avelumab, sintilimab, tislelizumab, and ipilimumab, have been given the green light for use in combination with targeted therapy in the treatment of advanced gastric tumors [25].

1. **Immune Checkpoint Inhibitors:** Ipilimumab was the first ICI to treat melanoma to receive approval in the globe in 2011 [28]. Since then, immune treatments have completely changed the approaches to treating advanced stomach cancer. Three categories of ICIs, anti-PD 1/PD-L1 and anti-CTLA4 antibodies, predominate [29]. T cells and other immune cells that are activated can express PD-1. When PD-L1, the ligand for PD-1, binds to PD-1, immunological suppression and immune cell death follow. In advanced gastric cancer, PD-L1 is overexpressed, which causes tumor cells to resist immune response [30]. However, CTLA-4 protein has the ability to bind with B7-1/B7-2 with high affinity, inhibiting the CD28 signaling pathway, which is essential for T cell activation [31].

Nivolumab, a monoclonal antibody that inhibits PD-1, was approved by the FDA in 2014 for the treatment of advanced gastric tumors [32]. Through phase III clinical studies done across 40 Asian nations, the effects of nivolumab against advanced stomach cancer were investigated [27]. According to preliminary findings, nivolumab dramatically improved patient survival rates when compared to placebo. The human immune system depends on CTLA-4 in important ways. Although CTLA-4 and CD28 are homologous, B7-1/B7-2 can interact with CTLA-4 with a higher affinity [31]. CTLA-4 can therefore control or even prevent CD28 signaling. Tremelimumab and ipilimumab, two CTLA-4 inhibitors, have been studied in clinical studies for advanced gastric cancer [26]. For the treatment of advanced gastric cancer, a combination therapy using ipilimumab and nivolumab has been approved.

2. **Adoptive Cell Therapy:** Specific neoantigens with a high immunogenicity can be expressed by gastric cancer cells, activating the human immune system. Cancer cells can be identified and eliminated in this manner. However, cancer cells have the ability to produce immune-suppressing substances such lymphocyte-activation gene 3 (LAG-3), TGF-, prostaglandin E2, and IL-10 that prevent immune response, enabling them to avoid immune system identification and removal [33]. Adoptive cell therapy has been shown to be a successful method of treating advanced gastric cancer in individuals whose immune systems are unable to recognize and respond to cancer cells [34]. In order to effectively induce immunity to eliminate cancer cells, adoptive cell therapy makes use of a variety of immune cells, such as tumor infiltrating lymphocytes (TILs), lymphokine-activated killer cells, and cytokine-induced killer (CIK) cells [22, 35].

3. **Anti-Angiogenic Therapy:** Vascular endothelial growth factor A (VEGFA), which is involved in the procedure of forming new blood vessels (angiogenesis),is of paramount importance in gastric cancer development. The modification of the immune response to cancer by VEGFA has the potential to allow tumor causing cells to elude the body's defense mechanism. Advanced gastric cancer patients treated with bevacizumab and ICIs like atezolizumab, ramucirumab, and durvalumab have shown favorable efficacy in clinical studies [25].

4. **Cancer Vaccines:** The use of cancer vaccines, whichh can trigger immune responses against tumor cells in vivo, is another new treatment for advanced gastric cancer [36].The most extensively researched cancer vaccines are mRNA vaccines, which quickly transform the genetic information of an antigen into a protein to trigger an immune response and the killing of cancer cells [37]. Studies have shown that mRNA cancer vaccines outperformed conventional chemotherapy or targeted therapy in terms of both efficacy and negative effects [38]. Furthermore, preliminary clinical trials have demonstrated dramatically increased cytotoxicity against tumor cells when cancer vaccines and chemotherapies like cisplatin and 5-fluorouracil are combined [39].Results revealed that heightened humoral and cellular response to vaccines peptides was present in 50% of the patients treated with cancer vaccines.

5. **CAR-T Cell Therapy:** The CAR-T cell is particularly made to express synthetic receptors that can cause T cells to recognize a particular cancer antigen, which then triggers the host’s immune system to kill tumor cells [40]. Gastric cancer can be diagnosed and treated with the help of biomarkers like claudin 18.2 (CLDN 18.2), human

epidermal growth factor receptor 2 (HER2), mucin 1, natural-killer receptor group 2 (NKG2D), epithelial cell adhesion molecule (EpCAM), mesothelin (MSLN), and carcinoembryonic antigen (CEA) [41].

IV. HEPATOBILIARY CANCER

The two types of cancer of the hepatobiliary system comprises hepatocellular carcinoma (HCC), cholangiocarcinoma (CCA), and gallbladder cancer (GBC),. Over 90% of liver cancer cases are hepatocellular carcinoma (HCC), which is the most prevalent kind [42]. One of the few tumors with rising mortality and incidence is HCC [43].The intrinsic and extrinsic malignancies of hepatobiliary tract or cholecyst is referred to as biliary tract cancers (BTC). Because the majority of BTC are asymptomatic until advanced stages, they are uncommon and aggressive malignancies [44].Studies and clinical investigations have examine the application of immunological therapies in HCC and BTC because of the dearth in efficient medications also the unique immunological milieu of the hepatic system[45].

1. **Immune Checkpoint Inhibitors:** With fewer undesirable consequences than cytotoxic chemotherapy, immune checkpoint inhibitors (ICIs) are shown beneficial in the systemic therapies of cancer. Inhibitory and stimulating immunoreceptors make up immunological checkpoints, which control the immune system. In order to generate an immunological milieu that is immune tolerance to the cells associated with tumors, tumor cells can upregulate the expression of proteins that bind inhibitory immunoreceptors or downregulate the expression of surface proteins that block the activation of stimulatory immunoreceptors. ICIs are designed to prevent the interconnection of immune as well as tumor cells to enhance immune cells' anticancer activity [46].

   The first CTLA-4 inhibitor for HCC was tremelimumab, a cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitor. The study showed that tremelimumab has a decreased efficacy and a tolerable safety profile. Theoretically, combined therapy may be more effective as a result [47].Nivolumab, a programmed death-1 (PD-1) inhibitor, is the earliest PD-1 inhibitor to be licensed by FDA to treat HCC in 2017,consequence in Checkmate 040 and Checkmate 459 trials [48]. A PD-1 inhibitor known as pembrolizumab has shown effectiveness in treating a number of malignancies. In the Keynote-224 trial, individuals with HCC who had progressed on sorafenib or were unable to tolerate it were treated with pembrolizumab. Pembrolizumab was effective and safe. Pembrolizumab was approved by the FDA in 2018 for treatment in advanced HCC,as the outcomes in clinical trials[49].

2. **Adoptive Cell Therapy:** Adoptive cell therapy involves harvesting tumor infiltrating immune cells from the patient and expanding them in the ex vivo setting. The harvested cells can also be genetically engineered for specific targets prior to expansion. After expansion, the cells are infused back into the patient.

   - **Tumor Infiltrating Lymphocytes (TIL) in HCC:** TILs are immune cells that have been collected, grown, and then reinfused into the patient with IL-2 to activate T cells. TILs are chosen for harvesting their capacity in detecting cells associated with tumors. The patient receives cydarabine/fludarabine for lymphodepletion prior to infusion. TIL is capable of identifying various antigens as well as being shown to be more successful in locating ,eliminating cells associated with tumors.

- **Tumor-Infiltrating Lymphocytes for BTC:** TIL is a field of BTC therapeutic investigations that is still being developed [50]. A unique and complicated microenvironment exists in BTC, including CCA, which promotes immunosuppression and the growth of tumor cells.The existence or lack of tumor infiltrating lymphocytes , CCA can be categorized into two groups. Immune cell infiltrate tumors are typically more sensitive to treatment [51].

- **Chimeric Antigen Receptor T Cell (CAR-T Cell) in HCC:** Employing genetic engineering, chimeric antigen receptor T-cell (CAR-T cell) therapy uses patient-derived T cells to target certain cancer-related antigens. After being re-infused into the patient, these CAR-T cells recognize and bind the tumor antigens, which triggers their activation and cytotoxicity. By emphasizing on tumor-specific antigens that are hardly produced in healthy tissue, CAR-T cells can provide an optimum therapeutic benefit with fewer adverse effects. Numerous intriguing targets have been looked at in HCC, including AFP, GPC-3, MAGE, NY-ESO-1, hTERT, NKG2DL, EpCAM, CD133, CD147, and MUC1 [52].

- **CAR-T Cell in BTC:** Additionally, there are still a handful BTC targets that have proven effective, despite many HCC targets having been discovered. One potential target for CCA is mucin 1 (MUC1), which is abundant in malignant tumors and is correlated with a poor prognosis and survival. Suimon et al. developed a CAR-T of the fourth generation containing anti-MUC1 domains and evaluated the construct's efficacy in CCA cells. Based on the facts, it is possible to use MUC1 as a target for CCA therapy because it has cytotoxic and obstructing effects on cancer cells [53]. An intriguing target that is increased in CCA but not in neighboring epithelial tissues is integrin v6. Integrin v6 is strongly expressed in malignancies, and this has been linked with a reduced survival time. According to research conducted in vitro, targeting this antigen enabled substantial amounts of cytotoxicity in tumor cells[54].

3. Vaccine Therapy

- **Vaccine Therapy in HCC:** Treatment utilizing vaccines may take constructive advantage of the Polymorphism of HCC and the milieu of the liver immune tumor. Vaccines induce a T-cell-response by exposing antigens or dendritic cells with antigens. The focus of vaccine techniques may be on peptides that are known to be present in HCC, encompassing AFP, GPC-3, MAGE-1, NY-ESO-1, SSX-2, and hTERT. Neoantigens can also be utilized to make vaccines that are specially designed for particular patients. Neoantigens, which cause mutations in tumor cells, are distinctive protein Sequences that are distinct to the patient and tumor [55].In comparison to the control group, 60% of patients in a phase 1–2 vaccine trial utilizing dendritic cells with AFP, GPC-3, and MAGE-1 antigens experienced illness stabilization [56]. In a distinct phase 1–2 trial, 22 patients with early-intermediate HCC and compatible HLA haplotypes were evaluated for safety and efficacy of the HepaVac–101 vaccination that targeted numerous antigens. In 37% and 53% of patients, respectively, the vaccination induced an immune response against HLA-class I and II tumor peptides, indicating that its safety profile was acceptable [57].

- **Vaccine Therapy in BTC:** Another area of research that is developing is BTC vaccines. Similar to HCC, the liver milieu supports the vaccine development that specifically aims BTC, albeit it has been difficult to create an effective vaccine. DNA vaccination that focuses CTLA-4 and PD-1 in CCA has shown promise in rat models [58]. The tumor antigens CD247, FCGR1A, and TRRAP were chosen as promising targets for the creation of an mRNA vaccine.

V. NANO-DRIVEN IMMUNOTHERAPY FOR THE TREATMENT OF CANCER

The development of nanomedicine has provided an efficient replacement for the drawbacks of traditional immunotherapy. Numerous nanoparticle-based drug delivery systems have been created during the past three decades as means of administering anticancer medications, small interfering RNAs (si-RNAs), oligonucleotides, plasmids, cytokines, and antibodies to specific areas of the body [1]. Nanocarriers have received a lot of attention because they preferentially accumulate in tumors as a result of the increased permeability and retention (EPR) effect, which is a method for delivering anticancer drugs to specific tumors. Along with the EPR effect, nanoparticles can be modified with ligands to specifically bind to receptors overexpressed on the surface of cancer cells for active internalization and delivery of the therapeutic cargo. This reduces off-target effects while concurrently increasing treatment efficacy. By using nanoparticle-engaging delivery systems for immunotherapeutic chemicals that target the immune system and/or cancer cells, these advantages can be utilized for immunotherapy. Numerous studies have shown that adjusting the sizes, shapes, surface charges, and hydrophobicity of immunotherapeutic medicines successfully increased their distribution into tumor tissues or lymph nodes [4].

Additionally, nanoparticles have the benefit of enabling simultaneous administration of several immunotherapeutic medicines to the targeted areas, enabling multi-modal and more effective therapeutic activity. Using nanoparticles containing immunotherapeutic agents, controlled and stimuli-responsive medication release in response to intricate and immune-suppressive tumor microenvironments has also been impacted [1]. The main ways that nanotechnology-based immunotherapy inhibits tumor growth are through two distinct mechanisms: one involves triggering a powerful anti-tumor immune response during tumorigenesis, and the other involves enhancing tumor immune defense by modifying the immune suppression mechanism in the tumor microenvironment. Understanding the relationship between the immune system and smart nanomedicine has given the development of cancer treatments a strong boost thanks to the success of tumor immunotherapy.

VI. CONCLUSION

Cancer immunotherapy has an appreciable advantage over traditional cancer treatments in that it not only cures primary tumors but also metastasis and recurrence. Scientists have been able to investigate new methods for immunotherapies by recognizing the deportment of cancer cells, recognising target antigens, and explaining the pathways of the immune system. The understanding that the traditional methods for evaluating treatment options in the age of chemotherapy and targeted therapies might not be appropriate for the new immunotherapies evolved over time. With the intervention of affordable and potential therapeutics new approaches can be developed to bridge the lacunae surrounding the gray areas in the field of immunotherapy. the investigation of rational combinations of

immunotherapeutic agents and new immunotherapy technologies is being intensified to enhance response.predictive markers for cancer immunotherapy's anti-tumor effect and survival benefits are crucial.Nanomaterials, with their tissue-specific delivery function,large surface area, and adjustable surface chemistry, are increasingly used in this field. As a result, nanotechnology has enormous promise for enhancing the effectiveness of cancer immunotherapy.

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