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Review

Immunotherapy for Cancer: Strategies of Immunomodulation Therapy in Combination with Conventional Approaches

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Abstract

The disease that poses a major threat to human life is cancer. Although different treatment techniques such as chemotherapy, radiotherapy, and chemically driven drugs are used, they do not show expected results and cause many side effects, eventually leading to the death of patients. However, there is one approach that is promising is the consolidation of cancer vaccines and immunotherapy, in which tumor-specific antigens, tumor-associated antigens, antigen-presenting cells, and toll-like receptors play a major role. The approach involves vaccines that are approved by the FDA and has shown good results in the latest research studies.

Keywords: Antigen-presenting cells, cancer vaccines, immunotherapy

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Cancer, which spreads at a faster rate, poses a great threat to the people in both developing and non-developing countries. There are achievements as well as failures in the fight against the prevention of cancer across the world.[1] The goal is to prevent it permanently. It could become potent when the assets are limited, and there is a huge divergence in the initial stage detection, screening, and anticancer therapies.[2] In 2018, 18.1 million new cases and 9.6 million deaths due to cancer were reported across the world. The rates of occurrence and death vary between generations and countries. Overall, over 9.6 million human population dies of cancer every year across the world, and the rapid rate of increase in the new cases will end up in identifying 22 million new cases every year in another 20 years. Among the different types of cancer, the major prevailing cancer types are lung, breast cancer in females, prostate, and colorectal cancer. Of these, the most frequent and major cause of death is due to lung cancer followed by liver, stomach, breast, and colorectal cancer.[3]

Deaths due to different types of cancer have been reported in the literature: prostate,[4] breast,[5] colorectal,[6] lung,[7] liver,[8] thyroid,[9] and pancreatic.[10] Factors contributing to

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cancer are alterations in genes, inherited genetic defects, age, gender, environmental exposure (e.g., UV rays, chemicals/preservatives used in the food, and radioactive materials), lifestyle, and variations leading to mutations. Chemotherapy,[11, 12] radiotherapy,[13, 14] chemically driven drugs,[15] surgery,[16] and certain inhibitors like vemurafenib against BRAF mutant skin cancer[17] are a few clinical treatment methods.

Many studies have reported that an immune system can trigger progressive tumors immediately irrespective of the virulent factors. In renal and skin cancer, tumor-infiltrating lymphocytes inside the tumor show positive prognostic response,[18, 19] in colorectal cancer, CD8+ T cells show positive prognostic response, and in breast and ovarian cancer, tumor-infiltrating lymphocytes show positive prognostic response.[20]

Vaccines for cancer have a set of procedures that need to be considered for creation, multiplication, and promotion of immunity against tumors. In the last 100 years, more vaccines have been therapeutically applied to treat cancer and to control tumor antigens, antigen-presenting cells (APCs), and other immune signals of the tumor. The combination of cancer vaccines with conventional therapeutic approaches may lead to removing regulatory adoptive T cell suppression and improved clinical efficacy through co-stimulatory pathways. In particular, the combination approach can lead to activation of the immune modulate cells by rebooting the immune system, thus rendering tumor cells would be more susceptible to immune-mediated killing.[21]

Mechanism of Therapeutic Vaccines for Cancer

The main objective of the vaccines against cancer is the activation of CD8+ cytotoxic T cells as the ongoing research on mice upholds the therapy by these cells. The APCs capture the neoantigens from the vaccine and the dead cancer cells. Then, the activated APCs migrate toward the lymph nodes, and major histocompatibility complex (MHC) molecules exhibit the neoantigens to T-lymphocytes. The CD4+ T cells build up immunity contrary to cancers, and CD8+ cytotoxic T lymphocytes help in the direct killing of the cancer cells by degranulation process using granzyme and perforin.[22] The peculiar type of vaccination approach is the activation of CD8+ cytotoxic T cells linked with MHC class I. Vaccines are categorized in Figure 1 according to their modes of action.

Peptide Vaccines in Anticancer Therapy

A familiar way of vaccination against cancer is the transmission of the MHC class I antigenic determinants from tumor-associated antigens (TAA) to stimulate CD8+ T cell duplicates that can work against self-antigens.[23] The peptides

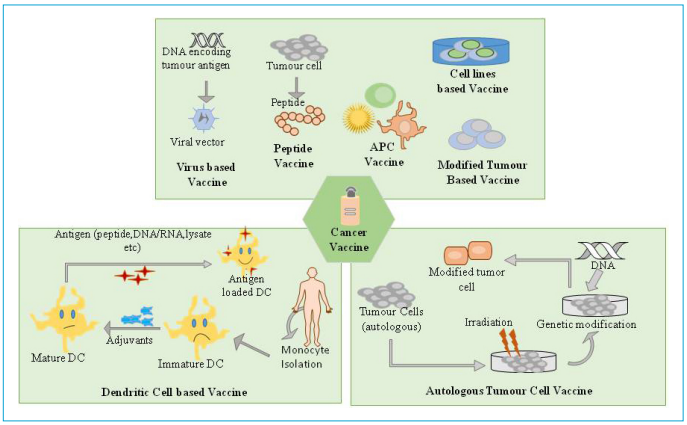

Figure 1. Different types of vaccines and their mode of action.

that are added inside the adjuvants, such as Montanide, which is similar to incomplete Freund's adjuvant (IFA), in the presence or absence of cytokines including granulocyte-macrophage colony-stimulating factor (GM-CSF), interferon γ, and toll-like receptors (TLR) have shown feedback partially or completely in different phases of clinical trials.[24]

Vaccines with one or more peptides can be infused with an adjuvant such as Montanide ISA-51 that is associated with cytokines such as GM-CSF to trigger APCs. This adjuvant has triggered TAA, in particular cytotoxic T cells. Cancer vaccines used in clinical trials are listed in Table 1. There is one challenge as IFA leads to the aggregation of T cells at the location of vaccination instead of promoting systemic immune response. Peptide vaccines are generally approved. The adjuvants and assembly of cancer vaccines are still ongoing. The advantages of peptide vaccines are they are easy to access, economically available at the mass level, and easy to be transported due to their stability.[25]

The second peptide that can show potent clinical effectiveness is synthetic peptide, which consists of MHC class I and MHC class II antigenic determinants.[26] A long peptide chain of length 23–45 amino acids infused subcutaneously proved efficient due to its processing and delivery pathway which triggers T cells.[27]

Vaccines from Antigen-Presenting Cells in Oncoimmunity Therapy

Studies on different sets of APCs such as activated B cells and peripheral blood mononuclear cells have shown great signs of progress and advancement. Dendritic cells have a mixed population of APCs, adopting antigens to suit their environment. Further, they prepare and display these antigens to CD4+ and CD8+ T cells and integrate immune response signals to counteract the secretion of cytokines, such as interleukin 12 (IL-12) which alter them to type 1 immune re-

Table 1. Cancer vaccines (2015 onward) used in clinical trials

Vaccine name	Targeted site of cancer	Functional malignant	Commercial producer	Current status	References	Web links
NeuVax	Breast cancer	Breast cancer with low to intermediate HER2 expression	Galena Biopharma, Inc.	Phase III	NCT01479 244	https://clinicaltrials.gov/ct2/show/NCT01479244
AVX 901	HER2+ cancer	Advanced or metastatic malignancies that express HER2	H. Kim Lyerly, Duke University	Phase I complete	NCT01526 473	https://clinicaltrials.gov/ct2/show/NCT01526473
INO 1400	Breast cancer	Multiple	Inovio Pharmaceuticals	Phase I complet e	NCT02960 594	https://clinicaltrials.gov/ct2/show/NCT02960594
GVAX	Pancreatic cancer	Metastatic pancreatic adenocarcinoma	Aduro Biotech, Inc.	Clinical phase II	NCT02004 262	https://clinicaltrials.gov/ct2/show/NCT02004262
SV-BR-1-GM	Metastatic breast cancer	Organ specific	BriaCell	Clinical phase II	NCT04418 219	https://www.clinicaltrials.gov/ct2/show/NCT04418219
DNA vaccine	Pancreatic cancer	Organ specific	Washington University School of Medicine	Clinical phase I	NCT03122 106	https://clinicaltrials.gov/ct2/show/NCT03122106
INO-5401 and INO-9012	Glioblastoma tumor	Glioblastoma (GBM)	Inovio Pharmaceuticals	Clinical phase 1/II	NCT03491 683	https://clinicaltrials.gov/ct2/show/NCT03491683
IFx-Hu2.0	Cutaneous melanoma	Specific	Morphogenesis, Inc.	Early phase 1	NCT03655 756	https://clinicaltrials.gov/ct2/show/NCT03655756
PIVOT-RCC	Renal cell carcinoma	Specific	Washington University School of Medicine	Clinical phase II	NCT03598 816	https://clinicaltrials.gov/ct2/show/NCT03598816
INVAC-1	Advanced solid tumors	Hematologic malignancies and solid tumors	Invectys	Clinical phase I	NCT02301 754	https://clinicaltrials.gov/ct2/show/NCT02301754
VGX-3100	Anal neoplasm	Anal/perianal high grade squamous intraepithelia lesion (HSIL)	Inovio Pharmaceuticals	Clinical phase II	NCT03499 795	https://clinicaltrials.gov/ct2/show/NCT03499795
INO-5401 + INO-9012	Urothelial carcinoma	Metastatic/recurrent urothelial carcinoma (UCa)	Inovio Pharmaceuticals	Clinical phase I/II	NCT03502 785	https://clinicaltrials.gov/ct2/show/NCT03502785
pTVG-HP	Prostate cancer	Nonmetastatic, noncastrate prostate cancer	University of Wisconsin, Madison	Clinical phase II	NCT03600 350	https://clinicaltrials.gov/ct2/show/NCT03600350
PROST VAC-V/F	Metastatic hormone-sensitive prostate cancer	Prostate	Washington University School of Medicine	Clinical phase I	NCT03532 217	https://clinicaltrials.gov/ct2/show/NCT03532217
VB10.16 immunotherapy	High grade cervical intraepithelial neoplasia	High grade HPV16+ cervical intraepithelial	Vaccibody AS	Clinical phase I/II	NCT02529 930	https://clinicaltrials.gov/ct2/show/NCT02529930
GX-188E	Cervical intraepithelial neoplasia	neoplasia (HSIL; CIN2/3) Cervical intraepithelial neoplasia 2, 2/3, or 3 (CIN3)	Genexine, Inc.	Clinical phase II	NCT02596 243	https://clinicaltrials.gov/ct2/show/NCT02596243
MEDI0457	Head and neck cancer	Metastatic head and neck squamous cell cancer	MedImmune LLC	Clinical phase I	NCT03162 224	https://clinicaltrials.gov/ct2/show/NCT03162224
VGX-3100	Cervical dysplasia	Multiple	Inovio Pharmaceuticals	Clinical phase III	NCT03185 013	https://clinicaltrials.gov/ct2/show/NCT03185013
GX-188E	Cervical cancer	Advanced, nonresectable HPV-positive cervical cancer	Genexine, Inc.	Clinical phase I/II	NCT03444 376	https://clinicaltrials.gov/ct2/show/NCT03444376
HPV DNA plasmid therape utic vaccine VGX-3100	Anal intraepithelial neoplasia	Human immunodeficiency virus (HIV)-positive	AIDS Malignancy Consortium high grade anal lesions	Clinical phase II	NCT03603 808	https://clinicaltrials.gov/ct2/show/NCT03603808
INO-3112 (MEDI0457)	Cervical cancer	Multiple	M.D. Anderson Cancer Center	Clinical phase II	NCT03439 085	https://clinicaltrials.gov/ct2/show/NCT03439085
VGX-3100, placebo	Cervical dysplasia	High grade squamous intraepithelial lesions (HSIL) of the cervix, associated with HPV-16 and/or HPV-18	Inovio Pharmaceuticals	Clinical phase III	NCT03721 978	https://clinicaltrials.gov/ct2/show/NCT03721978

Table 1. CONT.

Vaccine name	Targeted site of cancer	Functional malignant	Commercial producer	Current status	References	Web links
Personalized polyepitope DNA vaccine	Triple negative breast cancer	Organ specific	Washington University School of Medicine	Clinical phase I	NCT02348 320	https://clinicaltrials.gov/ct2/show/NCT02348320
Mammaglobin-A	Breast cancer	Organ specific	Washington University School of Medicine	Clinical phase I	NCT02204 098	https://clinicaltrials.gov/ct2/show/NCT02204098
CD105/Yb-1/SOX2/CDH3/MDM2	Breast cancer	HER2-negative stage III–IV breast cancer	University of Washington	Clinical phase I	NCT02157 051	https://clinicaltrials.gov/ct2/show/NCT02157051
pUMVC 3-IGFBP2-HER2-IGF1R	Breast cancer	Nonmetastatic, node positive, HER2 negative	University of Washington	Clinical phase I	NCT02780 401	https://clinicaltrials.gov/ct2/show/NCT02780401
Neoantigen DNA vaccine	Triple negative breast cancer	Organ specific	Washington University School of Medicine	Clinical phase I	NCT03199 040	https://clinicaltrials.gov/ct2/show/NCT03199040
pTVG-AR	Prostate cancer	Organ specific	University of Wisconsin, Madison	Clinical phase I	NCT02411 786	https://clinicaltrials.gov/ct2/show/NCT02411786
pTVG-HP	Prostate cancer	Hormone-resistant prostate cancer	University of Wisconsin, Madison	Clinical phase I	NCT02499 835	https://clinicaltrials.gov/ct2/show/NCT02499835

sponse, tumor necrosis factor (TNF), interferon γ, and IL-2, and improve the stimulation of CD8+ cytotoxic T cells.[28]

Vaccines from Dendritic Cells in Tumor Immunity

The clinical trials of these vaccines have proved to be uncommon as it involves ascertaining ways for vaccination. It is challenging to contrast clinical trials and analyze results regarding the efficiency of the trials. The tests have been performed on CD34+ progenitor cells, monocytes, tumor-specific antigens, TAA, and MHC class I peptides. These vaccines are infused inside the patient's body through the skin, blood, and lymph nodes. The advantages of these vaccines are they are cost-effective, nonhazardous, and they show good immune response. Suppression of tumors can also be seen in patients. The effective response of the clinical trials and immunology have been shown by dendritic cells harmonized with mucin 1-derived peptide and a mixture of PADRE peptides infused through the skin in patients suffering from renal cell carcinoma.[29]

The clinical trials performed on patients with skin and thyroid cancer are MART-1,[17] allogeneic tumor lysis,[30] autologous tumor lysis,[31] and transfection with RNA.[32] Those performed on patients with kidney cancer and breast cancer are vibrations with peptides[33] and fusion of allogeneic dendritic cells with autologous tumor.[34] For multiple melanomas, the clinical trials used are vibrations with carcinoembryonic antigen (CEA) peptide[35] and vibrations with mannan MUCI fusion protein.[36] For modification in pox, virus encoding CEA with Tricom is used.[37]

Modified Tumor-Based Vaccines

In previous studies, mice were vaccinated with destroyed tumor cells and transformed to show activation of immune cytokines such as GM-CSF.[38] The major role was played by tumor-specific CTLs, which investigated the cDNA libraries formed from tumor cell-derived mRNA and transfection took place in the MHC molecule of the recipient. This can be achieved by focusing on the T cell antigens, where the screening of peptides from MHC molecules takes place by the use of mass spectrometry and reversed-phase high performance liquid chromatography. The development of vaccines established on autologous tumor cells is achievable but complicated.[39]

Cell Line-Based Vaccines

Tests have been performed on allogeneic cell lines in the presence or absence of autologous tumor cells. The tumor cells explicitly increase GM-CSF, also known as G-Vax, which serves as an ultimate boost in the study where the patients having pancreatic cancer obtains recombinant listeria bacteria signifies the tumor associated antigen mesothelin in

presence or absence of G-Vax consisting of allogeneic pancreatic cancer cell lines.[40] Numerous vaccines are desirable without any hindrance from induced antibody and incorporation of bacteria present to act as abundant features of natural infection by activation of TLR and foreign pathogen receptors.[41]

Autologous Tumor Cell Vaccines for Immunotherapy

The cells can be taken into account for the transfection of APCs such as autologous or allogeneic cell lines with the genomic DNA of tumor. In this way, the undefined mutated genes in particular to tumor can be manufactured and conferred for triggering immune response. These vaccines are tedious to achieve from the patients who underwent surgery for a particular disease. The drawback is the production is limited to 2–3 doses of vaccines from the autologous tumor, and when there is availability of the autologous tumor, there is no consent about the processing, preservation, modification, and delivery for a candidate vaccine.[42]

Virus-Mediated Vaccines in Oncolytic Immunotherapy

Vaccines such as Gardasil and Cervarix used against human papillomavirus are certified against the virus. Their performance takes place by triggering humoral immunity in contrast to viral capsid proteins inside noncontagious viral-like particles. Adenoviruses can be treated as vectors precisely by infusing tumor antigens inside the muscle tissue.[43] These viruses are used in vivo to transform antigens into APCs and every virus shows rare results on the transformed cells from triggering to suppression of cells.[44] A favorable approach that has been approved is GM-CSF which acts as an adjuvant or as APC transformed growth factor inside the herpes virus vectors. The commonly used vectors such as T-Vec have been recommended for patients against skin cancer in phase III trials.[45] The clinical trials performed on the patients so far are: heterologous booster poxvirus tyrosinase for skin cancer[46] and poxvirus encoded 5T4,[47,42] heterologous booster poxvirus PSA and Tricom,[48] and poxvirus-encoded CEA and Tricom for kidney and colorectal cancer.[49]

Other vaccines that have been used in clinical trials are as follows. For skin cancer: NY-ESO-1 and Iscomatrix,[50] ganglioside, and IFA; for lung cancer: α GalCer PBMC with Interleukin-2 and GM-CSF,[51] transduction of allogeneic tumor with antisense TGF-β2,[52] and transduction of allogeneic GM-CSF mixed with autologous tumor;[53] for multiple melanomas: umbilical vein endothelial cells;[54] for pleura cancer: autologous tumor with GM-CSF;[55] for brain cancer: transduction of autologous tumor with antisense TGF-β2;[56] and for head and neck cancer: Hsp65.[57]

Other techniques employed for the treatment of cancer are tumor ablation, where the removal of large and small tumors takes place; radiofrequency ablation, which involves heating at particular locations, leading to inflammation and necrosis, and triggers the activity of natural killer cells;[58] and cryoablation, which involves the discharge of TAA, enhancing the immune response against tumors.[59]

One example of therapeutic vaccine against cancer is sipuleucel-T produced by Dendreon, which has been certified by the Food and Drug Administration (FDA). The therapeutic mechanism of the cancer vaccine is shown in Figure 2. Therapeutic vaccines have been authorized for the analysis of metastatic prostate cancer in the long-term survival in phase III clinical trials.[60]

How Does a Cancer Vaccine Work?

The definite responsive immunotherapy aims to trigger an immune response against the tumor by transmitting tumor antigens into dendritic cells and contributing the optimum requirements for the maturation of the dendritic cells inside an effective immune response of APCs. The four major steps describing the working of cancer vaccines are identification of tumor-rejection antigens, stimulation of a robust host's immune system, reducing the risk of autoimmunity, and evasion of the immune system (Fig. 3).

Identification of Tumor-Rejection Antigens

Tumor antigens are extracted from the cDNA library or from peptides as tumor-specific cytolytic T cells. The efficacy of the tumor antigens relies upon the prevalence and avidity of the T cells present inside the patient's body.

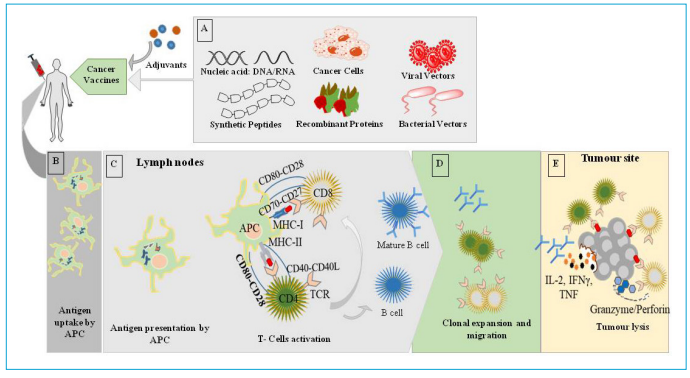

Figure 2. Therapeutic mechanism of vaccine for cancer treatment. **(a)** Various composition of antigen-specific cancer vaccine to deliver tumor antigen, **(b)** neoantigen taken by APCs at the vaccination site and then migrate to the lymph node, **(c)** antigen presentation by activated APCs to T cell through MHC-I and MHC-II and stimulation of B cell proliferation by T helper cell, **(d)** activation of antigen-specific CD4 helper and CD8 cytotoxic T cell leading to clonal expansion and migration to the tumor site, **(e)** killing of tumor cells.

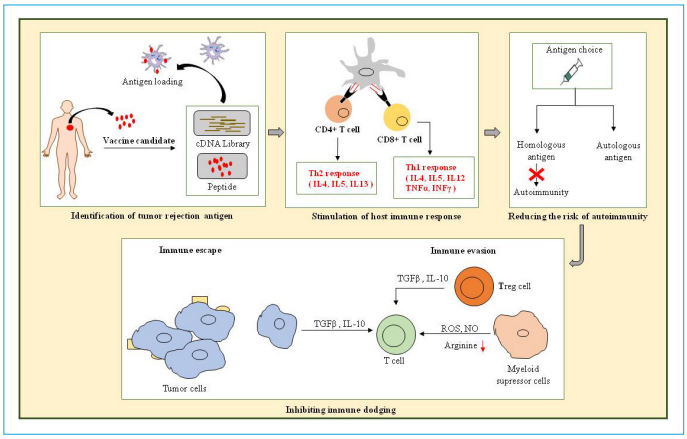

Figure 3. Role of cancer vaccine response to the immune system inside the body.

[61] Antigens vary in their efficacy in achieving immunotherapy. Very little or no tolerance is observed in tumor antigens related to fetal genes observed in immunological sites such as CEA, and MAGE family creates great tumor-rejection antigens. In the case of tissue-originated sites, MART1, ERBB2, and SILV show tolerance but uncertain tumor rejection antigens.[62] The major types of tumor antigens strengthen with the description of telomerase reverse transcriptase, which acts as a potent antigen in patients suffering from cancer. Few other tumor antigens are survivin and OFA. These antigens prove to be key for safeguarding oncogenic traits of the tumor cells, where immune dodging can be hindered.[63]

Stimulation of a Robust Host's Immune System

The objectives are to direct tumor antigens inside the dendritic cells and make the dendritic cells process antigens into robust stimulation of immune response. There are two pathways for dendritic cells: in vivo and ex vivo. The in vivo technique involves infusion of antigen combined with adjuvant inside the patient's body. It is easily understandable and most favorable. In the case of in vivo technique, dendritic cells are manipulated, and the loading of antigen will show the best distinction of action of the APCs. The research study shows that dendritic cell immunotherapy is efficient compared with other techniques. The CD4+ T cells provide immunity against tumor, cytokines such as interferon γ helps in the stimulation of tumor cells toward CTL lysis, enhancing MHC class I interpretation and internal pathway, which trigger the innate arm of an antibody at the location of tumor and hinder angiogenesis.[64] The CD8+ T cells consist of the effectors' arm of an antibody against the tumor reaction, from the information to reach an optimum result. CD4+ and CD8+ T cells are required to obtain immunity against tumor.[65]

Reducing the Risk of Autoimmunity

Proper methods need to be followed for vaccination against cancer, to infuse a therapeutic antitumor response and avoid the undesirable height of autoimmune results. The peripheral immune system is occupied by a range of autoreactive T cells categorized into two different groups: low avidity T cells and low-to-high avidity T cells, tissue-specific factors avoided by central and peripheral tolerance. In high avidity, autoreactive T cells are prone to threat.[66]

Evasion of Immune System

Tumor cells generally promote the activation of STAT1/B7H1 and the secretion of IL-10 and TGF-β factors that hinder the antitumor response. The genetic changes like mutations occurring in the tumor antigens make the tumor cells less viable to immune recognition leading to immune rescue.[66] The complication arises when mutations appear to begin in the antigen processing pathway like proteasome, TAP, and β2- microglobulin.

Combination Therapy: Immunotherapy and Cancer Vaccines

The sensible expansion of the vaccines and the immunotherapeutic ways for the medication of cancer involves the tumor microenvironment and immune response that determine the antitumor immunity. The suppression of regulatory T cells (Treg) builds up a risk for the patients to establish autoimmune diseases (Fig. 4). The consolidation approach of vaccines and immunotherapy brings about the stimulation of inhibitory pathways in the immunosuppressive microenvironment of a tumor. A positive report on consolidation therapy has been found, which focuses on numerous arrays inside the immune system to increase immunity against tumors. The efficiency of the dendritic cell vaccine against B16 skin cancer in mice models can be increased by gene silencing of TGF-β1, which decreases the regulatory T cells associated with tumor.[67]

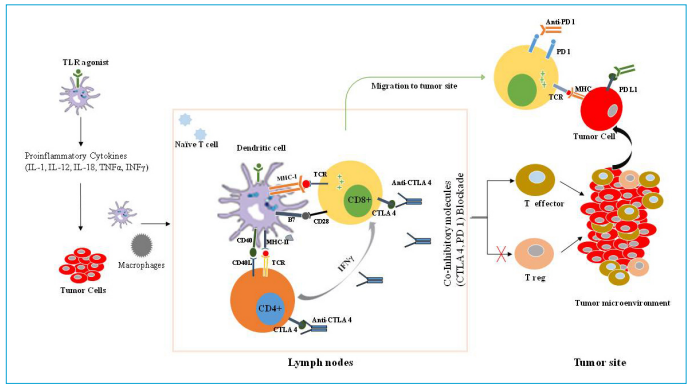

Figure 4. Future with the Combination use of cancer vaccines and immunotherapy to improve conditions against cancer.

The advantages of this consolidation approach overcome the immune checkpoint indicated in research studies that blockage of PD1/PD-L1 pathway by anti-PD-L1 to counteract the antibodies in addition to the exhaustion of regulatory T cells relapse the disease. The approach has proved one of the best therapies to suppress the tumor work against cancer.[68]

The challenges faced in the development of cancer vaccines are tumor immune suppression and antigenicity. The obvious fact is the immune response of healthy individuals and cancer patients work differently. The cancer patients have to negotiate for both specific therapy and the tumor type. Antigenicity, where the vaccines do not have a specific target to tumor antigens, leads to mutations due to certain factors such as lifestyle, genetic, and environmental changes.[69]

Nowadays, various new approaches are targeted toward immunotherapy and cancer vaccines, which include the combination of checkpoint inhibitors and personalized neoantigen vaccines. CTLA-4 inhibits the stimulation of T cells with the direct interaction of CD 80/86, where the T cell activation is stopped, leading to no immune response.[70, 71] This means the blockage of checkpoints was done via the development of the monoclonal antibodies as an approach toward therapeutics. Ipilimumab, an FDA-approved monoclonal antibody against CTLA-4, is used for the treatment of melanoma.[71, 72] In the previous research, it has been shown that checkpoint inhibitors have shown T cell responses and tumors carry huge mutational stress, which generates a lot of neoantigens.[71] Melanoma and nonsmall lung cancer usually have a high load of neoantigens, which tend to show positive feedback against checkpoint inhibitors and a good overall survival rate.[72–74] On the contrary, tumors exhibiting fewer mutations such as thyroid cancer and leukemia show a low overall survival rate.[75]

Another approach of cancer immunotherapy is to release the immune response through inhibition of checkpoint molecules with the use of inhibitors. Many of the patients do not respond well to immune checkpoint molecules, but they can benefit from the combination treatment of the inhibitors and antigen-specific therapy. CTLA-4, a checkpoint inhibitor, and Ipilimumab, the monoclonal antibody, have proved to lead NY-ESO-1 immune responses among patients with prostate, ovarian cancer, and melanoma.[76, 77] There have been reports showing melanoma patients treated with NY-ESO-1 in combination with Nivolumab. PD-1 inhibitor showed a 25% positive response among the patients.[78]

Future Perspectives of Combination Therapy

The most challenging task is to analyze precise dosage and efficient response in the combination of various checkpoint inhibitors including CTLA-4 and PD-1. Different components have been implemented for the blockage of PD-1/IDO/CTLA-4 pathways, which has shown encouraging results. This study combines the targeted therapies of the immune response with conventional therapies (Fig. 5) such as radiotherapy, chemotherapy, and chemically driven drugs to see the response on the cancer patients.[79, 80]

There are many issues that raise a concern about the type of antigen, whether TAA or neoantigens. TAAs are most commonly classified by tumors, but the limiting factor is the tolerance of the immune response, whereas neoantigens are tedious, expensive, and it is difficult to know the tumor changes in a patient. There are clinical trials using a specific antigen for vaccine, but no trial has checked the combined effect of TAAs and neoantigens on the activation of the immune response. This needs future research.[81]

Another aspect is combination therapy which involves the right therapies involved to have better results. It usually relies on the type of tumor, presence, and detection of biomarkers specific for patients. The use of vaccines applies as the last-line option. Therefore, to apply this process, we need to be sure about the dosage and the time for the immune response against a particular antigen.[82]

Humans and animals have dissimilarities in their immune response. Genetically engineered mice, xenograft, and orthotopic models are available to avoid this complication. However, there is a demand for big animal models, but it raises a concern for their breeding, ethical rules, and housing.[83]

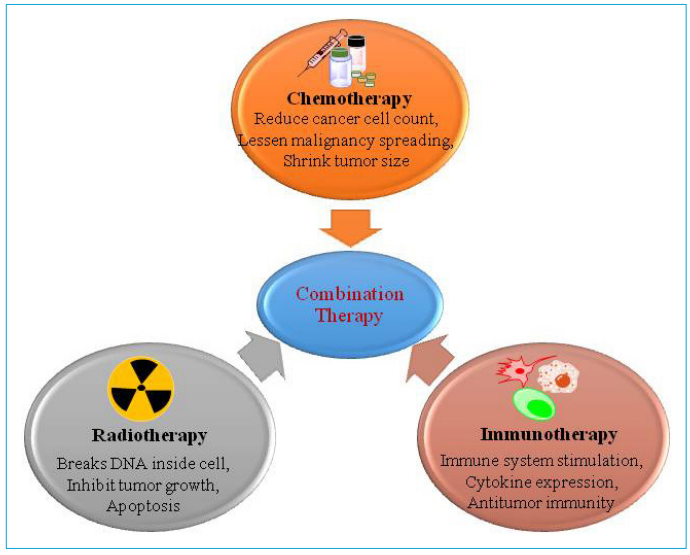

Figure 5. Combination therapy for cancer treatment.

Conclusion

To find a cure for cancer, the future lies in the use of a combination approach, cancer vaccines and immunotherapy, in which the risk of side effects is being reduced as compared with other therapies such as chemotherapy, radiotherapy, and certain drugs available in the market. Efficiency as well as the survival rate of the patients suffering from cancer is increased. However, many studies need to be performed to find a cure for cancer. The combination of personalized therapies is making a new direction toward an individualized patient's immune response and microenvironment with new techniques for the treatment of cancer.

Disclosures

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Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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