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# Advancement in Immunotherapy for Cancer Cells

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## Abstract

*Immunotherapy has always been scrutinized to its extent when it comes to having a promising cure for cancer. Advancement in this field is ever growing with the new immunomodulatory agents being discovered or modified along with their complete characterization extracted from plants and fungi as well. Due to the lack of complete understanding of either the structure or the mechanism by which they work, very few of them pass the clinical trial phases and reach the market. Nevertheless, scientists have not stopped working on understanding the tumor behavior and various immune responses related to it to come up with therapeutically potential immunomodulatory agents. Current agents are also being used in combination with other therapies to enhance the anti-tumour effect and to achieve better efficacy in the treatment. The intricate connection of immune responses and tumor behavior surely intrigues the scientists, which paves the way for better agents being poured Cancer Immunotherapy.*

**Key Words:** Immunotherapy, Cancer, Immune Response, Immunomodulatory Agents, Combination Therapy

## Introduction

Cancer is a disease where there is an uncontrolled division of cells in the body. It has been proved that there exists a complex and vast relation between the tumor growth and immune response of the body, and the tumor formation is a multistep process that can be altered by affecting the immune response (Reis et al., 2018). A specific system of check and balance regulate immune response to provide effective protection and tolerance (Sharpe, 2017). Immunotherapy is an efficient therapeutic candidate for treating cancer with increased drug approvals after clinical and pre-clinical development (Riley et al., 2019). Immunotherapy has improved the treatment strategies for cancer providing durable and control of previously incurable and fatal cancers (Fukumura et al., 2018).

Conventional ways of treating cancer such as surgery, chemotherapy and radiotherapy have still not provided complete satisfaction in the treatment due to the limitations and heterogenicity of the tumors (Shan et al., 2020), but immunotherapy is under research to discover its full potential, which requires an understanding of tumor behavior, microenvironment and the factors of the host which determine the response to immunotherapy treatments (Esposito et al., 2019). The role of the immune system in different cancers is explained in The Cancer Genome Atlas (TCGA), which hints towards the importance of the connection between immune responses and tumor behavior. (Goldsberry et al., 2019).

## Immunomodulatory Agents

### VEGF Family

The VEGF family is concerned with the development of blood vessels and epithelial ducts., VEGF-A is the

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most important member of this family, which promotes angiogenesis and vasculogenesis during normal physiological conditions. It also works for the development of embryo and tissue repair. In cancer, patients "angiogenic switch" occurs to aid in tumor growth. As growth increases, oxygen supply is reduced and results in hypoxia; therefore causes the production of proangiogenic factors like VEGF A, Production of VEGF is due to a method initiated by transcription factor hypoxia-inducible factor (HIF)-1. The new vessels formed underneath the influence of VEGF allows the growth to complete its nutrition demands. However, vessels formed are abnormal, deformed and irregular in shape. (Neufeld et al., 1999).

As tumors require new blood vessels for metastasis, it was considered that if we inhibit the angiogenesis, growth tumor may decrease and may improve the condition of cancer patients. Administration of VEGF-A or VEGF-R inhibitors decreases neoplasm growth in both human and animal models. 3 subclasses of drugs targeting the VEGF-A pathway have been introduced (1) tyrosine kinase inhibitors (TKIs) targeting VEGFRs, for example, sorafenib and sunitinib. (2) monoclonal antibodies like bevacizumab (acts on VEGF-A) and ramucirumab (acts on VEGFR-2); and (3) aflibercept, which is a fusion protein (acts on VEGF-A, B, and PlGF"}

The difference between TKI and monoclonal antibodies and fusion proteins is that TKI attaches to proangiogenic molecules underneath the plasma membrane and monoclonal antibodies and fusion proteins attach to receptors on the plasma membrane. (Lapeyre-Prost et al., 2017).

## Monoclonal Antibodies

In cancer, the malignant cells have the power to escape the human immune system. The two ways by which cancer was treated in the past include either the removal of tumor or its destruction by radio or chemotherapy. But at present a class of monoclonal antibodies at suitable targets shows control of autoimmune diseases and cancer. IgG1 is the antibody class mostly used for immunotherapeutic effect.

At the receptor site, antibodies bind to the antigen and block the signalling pathway to stop the tumor development by stopping the cellular growth.

ADCC is a process in which antigen-expressing cancer cells are killed when antibodies signal the NK cells, leukocytes, and macrophages directly. The process starts when Fc receptors on NK cells get attached to monoclonal antibodies at the Fc portion. Nk cells form a synapse with the tumor cells and release perforin and granzyme, which cause the death of the tumor cell. (Zahavi & Weiner, 2020).

The classical complement pathway starts when the fc portion of the antibodies gets activated when C1 binds to it and results in C3a and C3b formation. C3a becomes the part of immune effector cells, and C3b forms C5 convertase through the activation of the alternative complement system. Cell lysis occurs when the membrane attack complex is formed.

Monoclonal antibodies have shown the ability to change the immune response in cancer patients by blocking the function of receptors such as PD 1. This approach is now used in therapeutics for cancer.

Cytotoxic T lymphocyte antigen-4 (CTLA-4) binds to CD80 and CD86 on antigen-presenting cells. It acts as a negative regulator of T cells. Ipilimumab is the first approved complete human monoclonal antibody. The binding of CTLA-4 with its ligands is inhibited. This has shown a promising effect in advanced melanoma on phase 3 trials.

Activated T cells, B cells and NK cells have a transmembrane protein called PD-1 (programmed cell death ligand-1 or CD279). PD-1 binds to PDL-1, which interacts with CD80. PD 1 binds to PDL 2, which reacts with repulsive guidance molecule B. All these interactions block T cell. For this purpose, if an antibody suppresses PD 1 anti-tumour effect can be induced. (Hafeez et al., 2018).

## CAR T cell Therapy

CARs are antigen receptor proteins that have an antigen-binding region and TCR signalling domains. When CAR t cell therapy is given to patients, it increases the T cells effect and causes cytokine production and cell lysis. CAR is encoded by a retrovirus or a lentivirus to genetically modify the T cells, and then these are transferred into the patients. (Feins et al., 2019).

CARS targeting CD19 have shown the most promising effects during CAR T cell therapy in refractory pediatric and adult B ALL. During various

clinical trials carried out, CD 19 CAR therapy shows a 70 – 95% complete response. (June et al., 2018).

For further improving CD19-CAR therapy for the treatment of CD19+ malignancies, we need to select new tumor antigens for different types of cancer.

Tumor specificity of a CAR is an important factor that needs special consideration. At the time CAR is registered for 30 tumor antigens in clinical and pre-clinical trials.

While selecting the CARS target, there are many concerns that should be considered, including a role in oncogenicity, expression level, immunogenicity, the expression on cancer stem cells, specificity, the number of patients with tumors expressing the antigen, the number of epitopes and cellular localization.

It has been seen that CAR T cell therapy works by destroying by CD 19, and it also removes CD 19 immunosuppressive regulatory B cells. CAR therapy is not yet FDA-approved, but such approval is anticipated for CD19 CARs, which will surely prove beneficial. (Lohmueller et al., 2017).

## Therapeutic Cancer Vaccine

Over the past decade, recent advancement in cancer immunotherapy has increased worldwide, and novel medical techniques and formulations are passing the trials to become a candidate for the treatment of cancer. As prescribed for other diseases, scientists and researchers think that vaccination may be an effective immunotherapy method and prevent overgrowth or abnormal cell division (Xu et al., 2017).

Vaccines have greatly revolutionized the treatment strategy in the eradication of smallpox and other diseases from the world, thus, decreasing the global burden of the disease in return (Zhang et al., 2018). Regardless of killing a tumor cell with poison or radiotherapy, the vaccine has become a part of the treatment of cancer by inducing and boosting up the immune response against the tumor cells (Xu et al., 2017). Therefore, vaccines are being designed for different types of cancer, including cervical cancer, prostate cancer, melanoma, colon cancer and breast cancer, since many traditional types of vaccines are being tested, including DNA vaccines, mRNA vaccines and many more (Zhang et al., 2018).

Different kind of vaccines has proved very satisfactory regarding safety profiles, manufacturing, and quality control as well. Peptide vaccines, subunit vaccines with targeted or delayed-release vaccines are tested in clinical trials. [10] Therefore, the advancement in cancer immunotherapy has marked decreasing prevalence of cancer and patient deaths around the world which would otherwise be recorded in more than few millions annually (Donaldson et al., 2017). The main problem associated with cancer vaccines is a delayed onset of action resulting in delayed observable clinical responses. The traditional practices included increasing the dose or neglecting the delay, but ongoing clinical trials are majorly focused on combining this drawback with the effective release response of vaccine to get the optimum therapeutic effect (Xu et al., 2017).

Generally, the vaccine that is ready for clinical trials involves 3 basic steps.

1) Source material,

2) Target Prediction,

3) vaccine manufacture.

The vaccine manufacture and cancer immunotherapy, which has been a primary factor to be focused on where the global burden of cancer is considered, has evolved through multiple trial and error methods and improved techniques used one after the other. Whether single or combined therapy, it ultimately requires efficient planning and development of effective clinical trials for the vaccine candidate (Hu et al., 2018). Even though vaccines are passing clinical trials for evaluation of effectiveness, treatment, and cross-checking of the mode of administration and in the near future, hopefully, mankind can expect a vaccine treatment of cancerous cells. However, vaccine formulation and clinical evaluation have many barriers to overcome. For a vaccine to be effective against cancer cells, it must be able to initiate and induce the body's normal immune response (Fig. 1), which otherwise is decreased or suppressed by cancer cells. A successful vaccine formulation consists of the following components.

Table 1. Components of Cancer Vaccine.

| S. No. | Component | Features |
|---|---|---|
| 1. | Tumor antigens | Tumour-associated with/ tumour-specific |
| 2. | Formulations | Cell-based / viral based/ Nucleic acid based |
| 3. | Immune adjuvants | TLR* agonists/ saponin based/ DC* targeted monoclonal antibody |
| 4. | Delivery vehicles | Emulsions/ liposomes/ virosomes/ Nano discs |

*TLR, Toll-Like Receptors; DC, Dendritic Cells (Hu et al., 2018; 10)*

## Polyphenols

More than 8000 known polyphenolic compounds in foods have a much greater influence on nutraceuticals (Focaccetti et al., 2019) and proved themselves as one of the game-changer immunotherapeutic compounds by altering the level of cytokines, immunomodulators and other inflammatory mediators. Chinese people utilize polyphenols in plants, and the compounds have a significant role in the increased survival rate of patients with different types of cancer (Gomez-Cadena et al., 2016).

Polyphenols have a marked effect on the oncogenic activity and reducing the localized inflammation caused by tumor cells, thus affecting tumor growth (Focaccetti et al., 2019). Immunogenic cell death (ICD) has been discovered as a death that may Be caused by such polyphenols and drugs showing an optimum response, particularly when there is an established immune response against tumor (Gomez-Cadena et al., 2016).

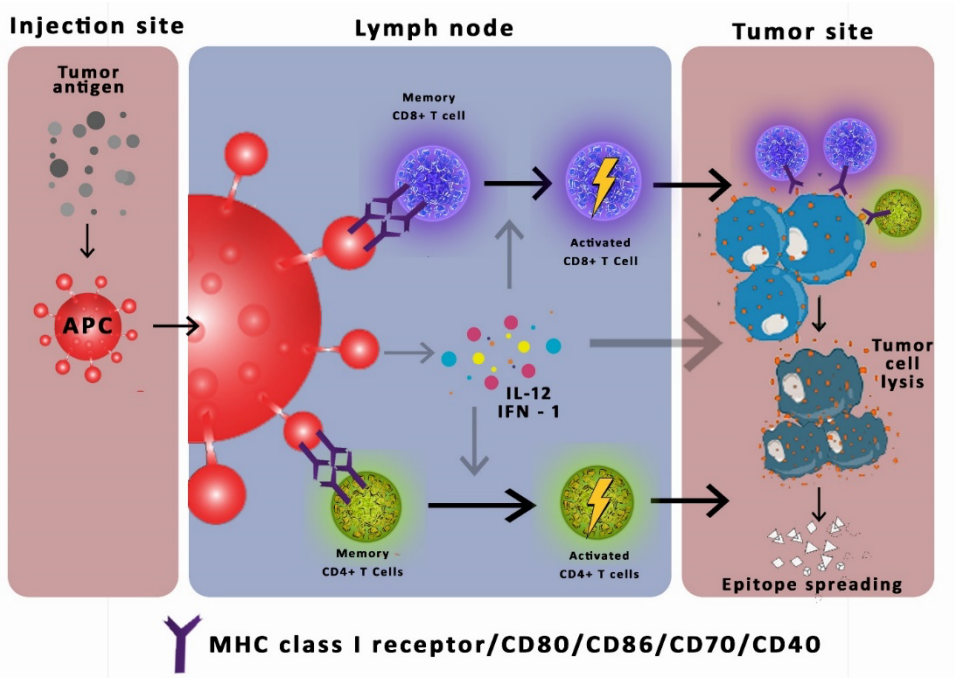


**Fig 1:** Mechanism of Action of Injected Cancer Vaccine Combined with the Body's Natural Immune Response

Polyphenols have been proved a successful candidate for the treatment of various kinds of cancers, e.g., colorectal cancer and have potential anti-inflammatory and anti-tumour properties that may block the molecular pathways of growth of tumor cells (Mileo et al., 2019).

Polyphenols may act as an antioxidant and anti-inflammatory agent. Their activity is generally

mediated by scavenging free ROS, downregulation of NF – Kappa B, iNOS, IL-8 and IL-6; regulation of T regulatory cells balance with IL – 17, IL – 6, TGF – Beta 1 (transforming growth factor-beta 1), reduction in the production of interferon-gamma (INF – gamma) and Tumor necrosis factor-alpha (TNF – alpha) (Mileo et al., 2019). Polyphenols efficacy generally depends on the state of target cells, whether they are activated, their oncological state (normal cells and cancer cells), dose, duration of treatment and pharmacokinetic properties (Focaccetti et al., 2019). The literature search demonstrates that more part of research and studies must be focused on polyphenols as they may prove to a mainstream therapy for the treatment of cancer. A more futuristic (Focaccetti et al., 2019) the approach is combining polyphenols' immune-boosting response along with drugs that can target tumor cells with the immune system synergistically (Focaccetti et al., 2019; Mileo et al., 2020). Some of the polyphenols that may prove beneficial in cancer immunotherapies are resveratrol, curcumin, chlorogenic acid, gallic acid etc. (Focaccetti et al., 2019; Gomez-Cadena et al., 2016; Mileo et al., 2019 #40). (Fig. 2)

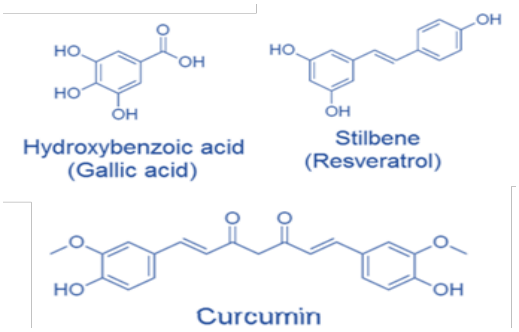


**Fig 2:** Chemical Structures of some Polyphenols

## Type 1 Interferons

Interferons, first approved by FDA to be used clinically as immunotherapeutic agents (Aricò et al., 2019), are a wide class of compounds that are involved in first-line defensive compounds released in response to any pathogen (B. X. Wang & Fish, 2019). While we uncover IFNs types, IFNs can be divided into most studied IFN-alpha and IFN-beta along with IFN- gamma with some of the least understood IFN types (Corrales et al., 2017).

Signalling receptors of IFN type 1 includes heterodimer receptors in both IFNAR1 and IFNAR2 receptor chains. Activation of these receptors initiates a cascade of phosphorylation reactions and lead to anti-inflammatory properties of IFNs. IFNs, having antiviral and anti-inflammatory tendencies, are thoroughly screened and studied for their role in any viral and bacterial infection. To retard the growth of tumor cells, interferon is produced by both normal and tumor cells. (B. X. Wang & Fish, 2019; Corrales et al., 2017). The anti-tumour effects of interferons have a marked significance in research and study since they were established some 50 years ago, however mechanism of action was unknown, and ever since they have been an under investigational research for use in cancer immunotherapy (Aricò et al., 2019).

Studies have revealed that IFN1 is induced in lymph nodes, tumour-infiltrating dendrite cells and myeloid cells, as well as leukocytes in tumor cells. (Aricò et al., 2019; Corrales et al., 2017). The discovery of the involvement of IFN1 in the signalling cascade and inhibiting the growth of tumor was a hallmark in the development of cancer immunotherapy (Corrales et al., 2017).

Even though interferons have established their significance in the treatment of all types of cancer by synergistically involving other methods of cancer therapy, however, their excess release may lead to some common symptoms including flu, myelosuppression, increased liver enzymes level, and neurologic effects

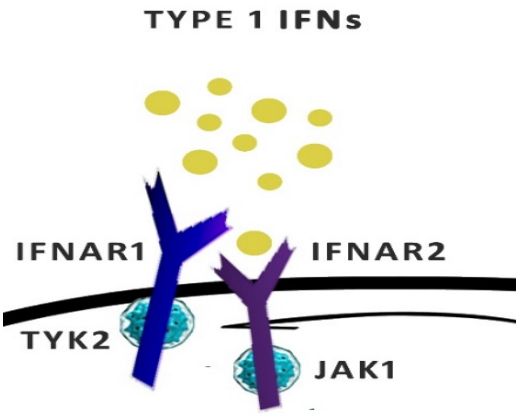


**Fig. 3:** Type 1 Interferons binding to their receptor sites leads to various signaling pathways ahead.

(Aricò et al., 2019). IFNs also caused severe toxicities in some patients, however some of the clinical trials stated their decreased toxicity level on changing the route of administration and dose strategies (B. X. Wang & Fish, 2019; Green et al., 2018).

Recent advancements in cancer immunotherapy also include IFN - gamma via intraperitoneal route of administration for the treatment of recurrent ovarian cancer in females (Green et al., 2018).

Despite the role in cancer immunotherapy as the first approved compound, IFNs therapy has been greatly replaced by novel therapeutic methods and compounds. Today, the shining era of interferon therapy demands re-thinking about its importance in cancer immunotherapy considering the novel therapeutics agents, combined with traditional IFNs therapy, along with the understanding of the mechanism of actions, for effective endogenous and external therapy to get the optimum treatment for any type of cancer. IFNs, normally considered as "dead drugs" may get their efficacy and place back in cancer immunotherapy with much better efficacy for patients at the right place, at the right time, at the right time (Aricò et al., 2019; B. X. Wang & Fish, 2019).

## Trichothecenes

Trichothecenes are sesquiterpenoids from the fungal genera produced by Fusarium, Stachybotrys and mesothelium. The changes in the parent ring structure divide the family into four groups (Bondy et al., 2000). Myrothecium verrucaria and taxa Myrothecium roridum have been investigated thoroughly for this trichothecene class and its analogues (Amagata et al., 2003). Myrothecine A is a macrolide compound extracted from the broth of Myrothecium roridum IFB-E012 (Liu et al., 2016). A family of non-coding RNAs-MicroRNAs (MiRNAs) play a role in enhancing degradation or arrest translation in the step post transcription. MiRNA plays a role in apoptosis, cell proliferation, differentiation, invasion, and migration. (Davis-Dusenbery & Hata, 2010). MiRNA demonstrated its role in lung cancer (Yamashita et al., 2015), human thyroid papillary carcinomas (Rosa et al., 2007) and prostate carcinoma (Galardi et al., 2007). Dendritic cells are responsible for not only exhibiting immune responses but also tolerance by governing T cell-mediated immune responses (Banchereau et al., 2000). Cytokines and other factors such as TNF, IL-4 boost the growth and differentiation of dendritic cells from myeloid progenitor cells. The level of dendritic cell maturation indicates the capacity to prompt a tumour-specific immune response (Steinman, 1991).

A study performed on myrothecine A not only exhibited the decrease in cell proliferation induced by miR221 but also the expression of miR221 was greatly reduced. It also reverses the downregulation of p27 caused by miR221 (Fu et al., 2019). The use of Mosher's ester and NMR spectroscopy data helped define the structure of two new macrocyclic trichothecenes and refine the characterization data of known analogues which can be further used in immunotherapy (Kao et al., 2020).

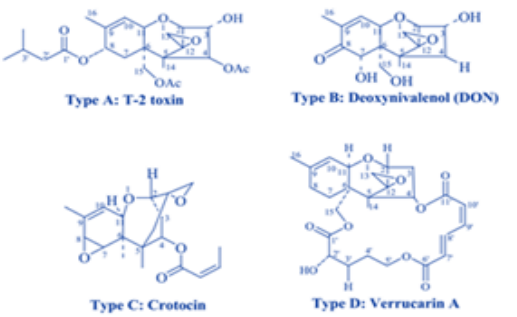


Fig. 4: Chemical Structures of trichothecenes. (Wu et al., 2017).

## Wnt inhibitors (wingless related integration)

The Wnt pathways are signal transduction cascades that regulate the development of embryo, homeostasis in adults, stem cell control and repairment of wounds (Clevers & Nusse, 2012). The Wnt ligand consists of glycoprotein with 350-400 amino acids in length. These are a total of 19 in number and are present across many species (Kusserow et al., 2005). These ligands may act as a directional growth factor and affect gene expression and may bring changes in the cell cytoskeleton or the growth of the cell overall (Rios-Esteves & Resh, 2013). Due to the important role this pathway has in various mainstream reactions, it becomes a very potential therapeutic target for many reasons. It has a role in cellular regulation, and even at the congenital level, malformations can occur due to disturbance in this pathway. There are either

pathway inhibitors or enhancers that work (Goldsberry et al., 2019).

Some genes or proteins are thought to affect or antagonize the Wnt signalling pathway, which includes DKK1, which is a member of the family Dickkopf (DKK) family of proteins which has a proposed mechanism of antagonism of LRP5/6 ligand (Cruciat & Niehrs, 2013). There are many postulations about the mechanism of DKK protein working by initialization or degradation of the LRP6 complex. While it is considered to be tumor suppressive, it may have a role in support of tumor growth (Kagey & He, 2017).

The negative feedback regulation of these target genes causes the degradation of Wnt receptors. These genes are Rnf43 and Znrf3 (Hao et al., 2012). These inhibitors require further investigation and may further be used for the therapeutic efficacy against cancer (Goldsberry et al., 2019).

## Immune Checkpoint Inhibitors

Recent studies have shown the inhibiting the signalling pathway or immune checkpoints can help alter the immune response (Mullard, 2013). while it is being believed that immune response alteration can work in cancer treatment, the cellular mechanism is still being studied (Hanahan & Weinberg, 2011). For the process to proceed it is necessary to understand the inhibitory step, for examples, the cytotoxic T cell recognition of cancer (Chen & Mellman, 2013). Different immune checkpoint targets are CTLA 4, and the drug acting as an inhibitor is Ipilimumab and PD1 is Pembrolizumab (Dine et al., 2017 ).

The overall major focus is on the programmed cell death proteins PD1 and PD2, which play a major role in suppression of immune responses, which are T cell-mediated (Okazaki & Honjo, 2007). The PDL2 binds with PD1 and are expressed on the APCs. The cells that can express PDL1 include tumor, dendritic and epithelial cells. When PD1 is ligated the downstream signaling and activation is inhibited. The expression of PDL1 is upregulated in the setting of interferon gamma (Wilky, 2019). The immunogenic cell death of tumor releases some antigens which are presented by the APCs to activate the immune response. If PDL1 is expressed to stop immune destruction at this final step, it is assumed that starting steps are intact and if not, then there are defects in the initial steps (Adams et al., 2019).

## Combination Therapy

### Combination with Chemotherapy

The anti-cancer effect of chemotherapy also depends on the cell death of cancer cells by the immune response. This results in immune-stimulatory signals through activation of the innate immune system by pattern recognition receptors such as toll-like receptor 4 (TLR4). This study has helped us in the development of combinational regimens containing both chemotherapeutics and immunotherapeutic using PD-L1-blockade together with chemotherapeutic. These combinations are used to treat lung and breast cancers and have shown promising effects. (Kruger et al, 2019).

## Combination with Radiotherapy

Production of non-irradiated lesions after radiotherapy is known as the “abscopal effect”. This abscopal effect is linked to immunogenic response, but it is still not clear. Many strategies are now understudied to cleave the immunogenic response of radiotherapy (Kang et al., 2016). Exposure of the tumor specific antigen occurs after the radiation therapy, which makes them visible to the immune system; as a result, cytotoxic t cells are activated. Radiations also help in the infiltration of immune cells. This relationship is the rationale for combining radiotherapy and immunotherapy. (Y Wang et al., 2018).

The placebo-controlled, phase III trial was done in which anti PD L1 was combined with platinum-based chemoradiotherapy. this study showed that PD 1 blockade given within 14 days of radiotherapy was more promising than giving it later than 14 days. (Kruger et al., 2019; Xu et al., 2017).

## Combination with Immunomodulatory Drugs

The first-ever CPI confirmed for clinical use was Ipilimumab, targeting CTLA-4. After the success of Ipilimumab and PD-1-blockade, the combination of PD-1 and CTLA-4 blockade is the most investigated combinational approach.

Due to the success of ipilimumab and PD 1 many other combinations are under study. But it may occur that the agents show an antagonistic effect

rather than synergistic, so critical selection strategies based on testing are important.

Based on pre-clinical and early clinical data for simultaneous targeting of CD40 and PD-1 / PD-L1 in pancreatic cancer, a phase I trial investigating the combination of CD40, durvalumab and chemotherapy was initiated which showed promising effects. (Kruger et al., 2019).

## Perioperative Use

Currently, CPIs are mainly used in advanced tumor stages. The baseline tumor burden marks the efficacy of checkpoint blockade, enhancing the importance of perioperative use of this blockade therapeutically. In Europe, nivolumab was the first checkpoint inhibitor approved for the treatment of melanoma patients based on a clinical study. The study held a comparison between nivolumab and Ipilimumab for treating patients having melanoma at stage lll-lV. The observation was that patient treated with nivolumab had less severe adverse events with recurrence-free survival to be an important advantage. (Kruger et al., 2019).

## Cancer Immunotherapy Toxicity

In recent years where cancer immunotherapy has breakthrough effects in treatment of cancer, improving the QOL and sustainable progress in health recovery, nevertheless, successful cancer therapy never came without side effects. Apart from radiotherapy and immunotherapy some other treatment methods may induce major or minor toxicities in various organs, including pulmonary (Rashdan et al., 2018), endocrine (Chang et al., 2019), cardiovascular, dermatologic, neurotoxicity and few others (Kennedy & Salama, 2020).

Organ toxicity involves major side effects induced from over or wrongly activation of tumor cells by radiotherapy or other immunotherapeutic agents, or maybe due to the tumor cell resistance to extrinsic therapy. Therapeutic agents in cancer have become a "double edge sword" in almost every organ, including toxicities in GI tract (colitis, hepatitis), endocrine toxicity (hyperglycemia, hypophysitis hypopituitarism, hypothyroidism, hyperthyroidism, adrenal insufficiency (Chang et al., 2019), pulmonary toxicity (pneumonitis, sarcoidosis) (Puzanov et al., 2017; Suresh et al., 2018) and rheumatologic toxicity (Kennedy & Salama, 2020; Puzanov et al., 2017). In some rare cases of CVS hematologic and renal toxicity, ophthalmic and neurological toxicities also do occur (Kennedy & Salama, 2020; Puzanov et al., 2017). The current clinical trials of immunotherapeutic agents are more focused on the use of combined immunotherapy and radiotherapy, which is showing satisfactory results (Wirsdörfer et al., 2019). However, for previously established agents, careful handling is required in patients more susceptible to side effects and other toxicities. Medical oncologists need some evidence-based management of toxicities related to cancer immunotherapeutic agents. Only efficient management of toxicity may lead to effective therapeutic outcomes by all the promising candidates of immunotherapy.

## Conclusion

With the current advancement, one cannot surely say that immunomodulatory agents yet discovered can offer a complete cure for cancer but can mitigate and help treat various cancers to an appreciable extent. The toxicity profile has a major rule when these agents are used which restricts the treatment options for the patients. For these agents to work, there must be a proper understanding of the immune responses and the pathways involved in them to target the right step for tumor suppression. The immune responses are considered in detail by thoroughly understanding the factors involved, along with the exact pathway that is to be targeted. The factors responsible for the enhancement of inhibitory effect on tumor have a genetic basis which can be modified by genetically targeting such factors to either increase or decrease their effects. Apart from these immunomodulatory agents used alone, these are combined with other therapies and technologies to have better outcomes.

## Future Perspective

The scope of research and discovery in this field is beyond comprehension as new agents are adding so fast and have sound experimental data behind them that it becomes difficult to consider a single agent as most efficient for treating cancer. New agents are being discovered using the latest technologies that reveal their structures and characterize them to understand the mechanism by which they work. Many of the present agents are being modified and used to get better results. For even better

therapeutic outcomes, immunotherapy is being combined with other therapies such as radiotherapy, chemotherapy etc., to get even better results. The modification in delivery technologies is also very promising, with nanotechnology being used in targeting the tumor directly. This advancement is ever increasing, with new agents taking the place of older ones with less efficacy and more side effects. The new agents may be promising, but their toxicity and side effects are still a challenge for scientists.

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