A Review of Next-Generation Immuno-Oncology Agents for Cancer Therapy: Recent Dictation Shifts in Cancer Immunotherapy

By

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A thesis submitted to the School of Pharmacy in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy (Hons.) at Brac University.

School of Pharmacy

Brac University

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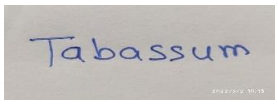

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Approval

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Abstract

The main aim of cancer immunotherapy treatment is to increase body's own immune system to wreck the tumor cell, and to reboot the immune system, enabling it to attack the tumor cells. Cancer immunotherapy along with Adoptive T-cell, Immune checkpoint inhibitors, Combination treatment has apparently well-established method for treating malignant melanoma as well as different malignancy. Despite having immense clinical evidence over different cancers, immunotherapy treatment methods have demonstrated a little impact for cancer patients. In reality, thus it is evident that some of the patients shows relatively low responses because of immunological disorder. Fortunately, in recent times a combination of cancer immunotherapy along with other cancer treatments have shown a tremendous result in clinical tests as well as the pre-clinical studies. In this article, four different types of immunotherapy techniques Adoptive T-cell, Monoclonal antibody, Immune checkpoint inhibitors, Vaccination have been reviewed. Furthermore, this project work attempts to look into the new directions in which immunotherapy is shifting and in future cancer patients can be benefitted.

Keywords: T-Cells, Immuno-Oncology, Antigen, Antibody, WBC, Checkpoint inhibitor, tumor

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List of Acronyms

WBC White Blood Cell

TAA Tumor Associate Antigen

TCR T-Cell Receptor

CD4 Cluster Differentiation 4

TSA Tumor Specific Antigen

TNF Tumor Necrosis Factor

MHCI Major Histo-Compatibility Complex

CDC Complement Dependent Cytotoxicity

ADCC Antibody Dependent Cellular Cytotoxicity

ADCP Antibody Dependent Cellular Phagocytes

Chapter 1

Introduction

1.1 Background

In recent times, the rate of cancer has increased gradually over at least the last 20 years, while death rates have shown a significant decline. Cancer treatment has undergone a gradual evolution since its inception in the 1800s (Carter; Thurston, May 2020). Immunotherapy is a cutting -edge treatment for cancers such as kidney, bladder, head and neck cancer, malignant melanoma, meager – cells, and lung cancer. There are four treatment options: surgery, chemotherapy, radiation, and targeted therapy (Franciscan Health; June, 2020). Chemotherapy works well in the majority of cases (Blackwell, 2015). However, immunotherapy has recently grown as a popular means of therapy exponentially in this era, and more extensive and advanced treatments are undoubtedly on the way in the near future. As the immunotherapy treatment process is complex, new strategies and skills are being developed progressively. Several aspects have been linked in this progression, the most significant one is the growth of thousands of monoclonal antibodies. In addition, researchers are developing a brand new method that includes the unicellular analysis to develop a large scale of DNA and RNA sequencing that can play a vital role for cancer treatment (Chen,Guo;2018).

However, several immunotherapeutic approaches have demonstrated a significant clinical value for many patients with different types of advanced cancer treatment. Nonetheless, we need more appropriate immunotherapies and predictive biomarkers for increasing the success rate of immune responses. The advancement of next generation sequencing technologies and their appeal in immuno-oncology will help tremendously towards this aim. In addition, immunotherapy treatment are now moving towards the realization of personalized medicine, thus, significantly increasing the expectations for a more successful management for cancer treatment (Guan, Li; 2012). Here, the study will further explain the current immunotherapeutic approaches against cancer including Monoclonal antibodies, Adoptive T-cell inhibitor immunotherapy, Vaccination, Immune checkpoint blockade and also analyze the roles of Cytokine in immune system, function of interleukin inflammation in adaptive immune responses. Finally, this review study will also discuss the different geographical and trends of

implementation of immune oncology therapeutic strategies as well as the comparison between the general cancer therapies as surgery, chemotherapy, radiation therapy and immunological treatment.

1.2 Immuno-oncology and how the immune system respond to cancer

Immune oncology involves harnessing the immune system to treat cancer (T Marshall, 2018). This study highlights how the immune system responds to cancerous cells and why it responds always in the way that is does. The immune system can recognize foreign micro substances as 'non-self' or unknown organisms and create a response to demolish the disease-causing agents. It can be played a same role for protecting the body from malignancy. The damaged DNA in cancer cells repeatedly directs the mutated gene that build up in cell as somatic mutation to yield abnormal cells known as tumour cells (Brosda, Sandra; 2020). Tumors are abnormal cell growth that may occur in any body part (Arneth, 2020). The body comprises with the dendritic cell, dendritic cells are the primary decision makers for determining the pathogenic substances and first encounter with the tumors cells (Fu and Jiang, 2018). Therefore the dendritic cells plays a significant roles for the preliminary immune rejoinder to pathogens. The dendrites cell moves and tries to kill the pathogens. The dendritic cell responds to pathogens by inspecting and attempting to kill pathogens via toll-like receptors (Tai; Reddy; Schneider, 2018). The recognition of the microbes induces pro-inflammatory cytokine production and improves antigen presentation to naive T cells, altering the antigen dealing with the adaptive immune response, which is the first step in the fight against tumors (Raeber et al., 2018). Tumors typically mutate to form antigens that are not normally found in body tissue (Chan et al., 2019). When tumor antigen-specific CDB + T cell activation occurs, the phagocytosed tumor antigen travels to the lymph node via various lymphatic vessels (Louie & Liao, 2019). Tumor antigen that has been activated migrates to fight tumors (Theisen et al., 2018). The activated tumor antigen migrates to fight tumors (Theisen et al., 2018). The tumor antigen is a result of a mutation in tumor cells generating different cellular proteins. The cytosolic processing of the cellular proteins gives rise to the formation of nerves peptides that are presented with class 1MHC molecules (Montealegre & van Endert, 2019). After that the regulation of the Major histocompatibility class (MHC) 1 expression allow the antigen either enter inside the cell or to leave it completely and to recognize the tumor cells (Cancer Australia, 2018). As, chemotherapy and radiation therapy can demolish the cancer cells directly but in case of immunotherapy it is unable to attack the cancer cells directly rather it helps to increase the body's' immune system to fight with the cancerous cells.

1.3 Different types of tumor antigens

The tumor antigens types are two; one is the tumor-specific antigens (TSAs) (Laumont et al., 2018.) or tumor associated antigens (TAAs) (Ovais et al. 2019). The TAAs are not specified to tumor cells and can be expressed on the normal cells to fetal development.

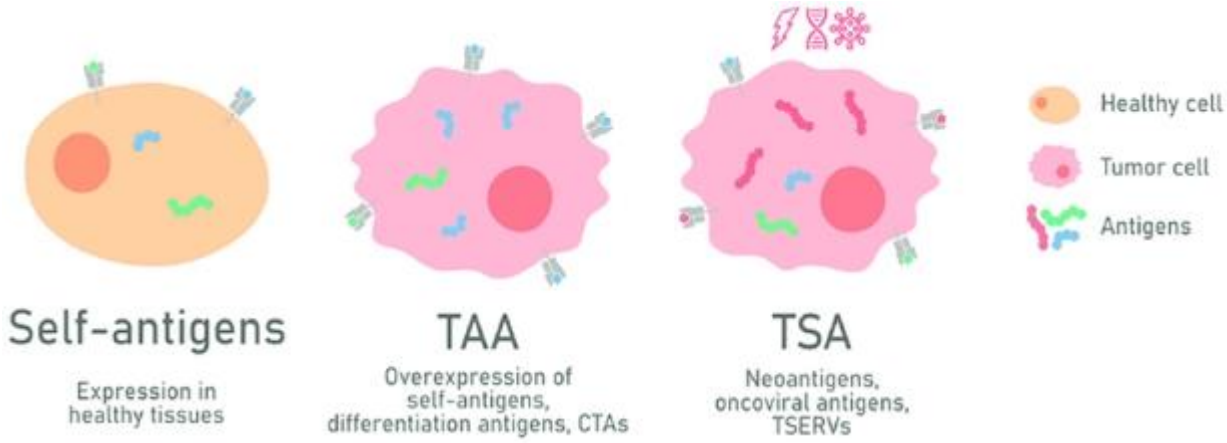

Fig:1.2 Illustrates self-antigens, expressed in healthy tissues, pictorial presentation of TAA-over expression of self-antigen, differentiation antigen, CTAs; TSA- neo-antigens, oncology viral antigens, TSERVs (Feola, et al.,2020).

The formation and development of T cells is the first step in the fight against infections. The red bone marrow produces T lymphocytes (Leone et al.2019). T cells are then pushed into the blood vessels and transported to the thymus gland (Nitta et al.2020). Herein for the development of the immune system thymus gland is an important organ. The thymus gland overlies the heart (Omura, 2017) and is the primary lymphoid organ (Kim et al., 2019). The thymus gland is the part that respond to the full development of T cells. The thymus glands usually produce mutate cells such as chronic lymphocytic leukemia or B cell lymphoma that help to draw the T cells into the thymus gland. The thymus glands typically operate during the early age of development, secreting the key mutates, which includes thymosins (Hall et al., 2009), thyroxine (Kato et al., 2017), and thymic factors (Yan et al., 2017). The chemical draws typically the T cell towards the thymus glands through chemotaxis (Dai et al., 2018). And as a result, the T cell starts moving towards the thymus gland. The T cell contains DNA (Sen et al., 2019). After that it produced by the thymus glands (thymosin, thymo factor) reacts with the T cell DNA to form a protein called RAG (Liu et al. 2019), which reshuffles DNA to produce different types of protein to form T - Cell Receptors (TCR) (Miyazaki et al., 2020). The TCR also activate another gene set to produce

CD8 protein (cluster differenciation8) and cluster differentiation4 (CD4). The T cell formed do interact with thymic cells to form CD8-MHCIand CD4-MHCII (Major Histocompatibility Complex). When there is successful recognition of thymic cells, a positive selection occurs, but otherwise, apoptosis occurs (Kuchler et al., 2017). Unsuccessful binding together of the cell leads to apoptosis (Jan 2019). If the T cell receptors bind together with thymic MHCII, a T cell undergoes apoptosis. Here it is formed by the thymic glands interacts with the T-cell to form TCR (T cell receptor (Yi et al. 2019). This causes the activation of RAG I and RAGII by the genes presented in the T cell (Delmonte et al. 2020). The RAG I and RAGII shuffle the DNA to produce TRC (T cell receptor), which differentiate types of protein for different types of antigens (Álvarez-Quilón et al. 2020). The TRC must recognize the antigen of different shapes that fit specific antigens. The chemicals also activate other Genes to produce CD4 and CD8 proteins (cluster of differentiation8) and cluster differentiation of protein (4). The process is continuous, and as a result, T-cell forms the TCR and CD8 (Drobek et al., 2018). Moreover, the thymic cell usually present specific types of molecular cells called MHC (Major Histocompatibility complex). CD4 binds perfectly with the MHII and CD8 binds with MHCI (major histocompatibility complex); the positive interaction of CD4 and CD8 to recognize the MHCII and MHCI, respectively, result in positive selection (Ostroumov et al., 2018). Failure for CD4 and CD8 to recognize the MHCII and MHCI respectively result in apoptosis. Additionally, when CD8 and MHCI do not bind together, apoptosis occurs. Additionally, T cell molecules can undergo a new series of binding in which the MHCI and MHCII molecules contain protein peptides which T cell can reception recognizes. If the TRC interacts, it can damage the immune system; when the TCR does not interact with the protein negative selection results, at that time an interaction between TCR and MHCI and MHCII happens. The apoptosis occurs again and the thymic cell secretes a chemical called TNF –alpha that initiates the apoptosis process. In the last stage, T cell becomes CD4 positive and TRC positive that is sufficient for interaction. In contrast, CD4 interacts with MHCII and fails to occur the cell downregulates CD4 molecules and then the T cell formed a cytotoxic cell. The thymatic cell can also interact to form CD4 and TCR with TCR molecules. The differentiation of T -cells as a helper cells and cytotoxic cell to form T-regulatory cells that can able to protect against the immune diseases. Some of the T-cells act as a helper cell and T cytotoxic cells are easily converted into T Regulatory cells for suppressing the immune response. However the Tumor- specific antigens (TSA) can only find into a cancerous cell whereas it cannot find in the normal cell. It can also help to make an immune response against cancer cell. Additionally, the Tumor- associate antigens (TAA) has an elevated level into the tumor cell and also it can express at the lower level on healthy cell.

1.3.1 Roles of cytokines in cancer immunotherapy

Cytokines plays a useful role in anticancer immune responses (Tkach et al). Cytokines are used in cell proliferation means the propagation of a T cell population through cell divisions (Thomas et al., 2021). Cytokines are composed of six families, which include interleukin one family (Rose-John, 2018), hemoprotein family (Bilska-Wilkosz et al., 2017), interferon family (Negishi et al., 2018), tumor necrosis factor family (Tafalla, & Granja 2018)), interleukin 17 families (Wojno et al., 2019) and IL-1, IL, IL-Ra, IL-18, and IL-33 are the part of chemokine species (Bonavita et.al, 2018). TL-2, IL-4, IL-5, IL-6, IL-12, and IL-13 are members of the hemoprotein family. G-CSF, GM, IL-14, IL-2, IL-2, IL-2, IL-2, IL-2, IL-2, IL-2, IL-2, IFN-B, IFN-Y, IL-10, IL-19, and IL-20 are all members of the Interferon family. The next family is the tumor factor family, composed of TNF, TNF-CD40L, Fas (CD95, BAFF, APRIL, LTi. In addition, the interleukin 17 family are composed of IL-17(IL17-A), IL17B, C, D, and finally is the chemokine family, which is composed of CCL19, CCL21, RANTES, CCL2, MCP1, CCL3 (MIP-1)

The interleukins family is mostly produced by pro-inflammatory organs, which secrete IL-19, IL-1b, IL-18, IL-33, and IL-36a, b, which means they cause swelling, whereas anti-inflammatory organs emit IL-36Ra, IL-37, and IL-38. The cytokine IL-Ra, IL-36Ra, and IL-37 L-38 belong to an interleukin family, which also possesses anti-inflammatory properties. The IL-1R 1 receptors bind to IL-1 (Divya et al., 2020). IL-1R is made up of the protein IL-IRACP (Tomita, 2018).The receptors belong to the 1G protein supper family, which are the same antibody members (Martinussen et al., 2021). At the cytoplasmic end, the IL-2R abandons MYD88 (Mylo Differentiation protein88) (Liu et al., 2019). The MYD88 interacts with TRAF6, which contains a significant cytokine known as IRAKS (Georg et al., 2020).MYD88 works as an adapter to allow the association of TRF6, which activates IRAK4 or IRAK6. IRAKs frees TAK from TAB1 and TAB2 (Mohammad & Thiemermann 2020)). The freed TAB allows the freeing of NFXB from IKKa, IKKY, and IKKP. The freed NF-KB moves to the nuclear for the production of specific gene saves the inflammatory molecules, which give rise to the inflammatory signs and symptoms.

However Cytokines act as a necessary immune regulators, cytokine-base drugs is also very impactful for cancer treatment. A large quantity of cytokines can be produced using eukaryotic or prokaryotic expression systems as the cDNA sequences of most cytokines that can make cytokines attracted to new drug development. In addition, the immune-regulatory mechanisms of cytokines can improve the efficacy and safety rates in cancer immunotherapy.

1.3.2 Function of IL-1, IL-2 and T helper immune responses in cancer immunotherapy

The importance of IL1, IL 2 and the T helper immune responses in cancer treatment is now well established (Baker, Brint; 2019). As for some cancers, the inflammatory conditions precede the development of malignancy. Possibly, aberrant signaling due to oncogenic mutations in tumors can result in a chronic inflammatory state developing as the proximal within the tumor cells. The chronic inflammation acts to inhibit the anti-tumorigenic immune response, normally mediated by cells such as CD4+ T cell. The function of CD4 cells plays a vital roles in mediating adaptive immune responses to several of pathogen as well as in tumor immunity. During the phage of TCR activation, a particular cytokine milieu, naïve CD4 T cells that can be differ from one lineages of T helper (Th) cells, including Th1, Th2, and Th17 to another. Cytokine production and function can define through the pattern (Santarlasci, Francesco; 2013).Moreover, the IL-1 moves to the liver to form specific acute phase proteins, which are important for inflammation. The hemato proteins family is significant for hemato function (Pandey, 2017). The hemoprotein contains a critical member, which is significant in the immune system. Hemato protein is a four-helix bundle structure. When T cell is activated, peptides present in the MHC or any other antigen present in the cell give rise to two signals to the proliferation of that cell. The interleukin functions in autocrine version, which helps the T cell undergo cell division (Jia et al., 2017). Naïve T cell will preliterate to form a cell termed as memory t-cell and effective T-cell. The IL-2R has three chains that is IL2RY, B, 9 (Damoiseaux, 2020). The IL2R appears in high affinity, which is a chain of IL2RB, Y, and 9. Secondly, the IL2R can also appear intermediates affinity which is the chain of IL2RY, B lastly, the interleukin two receptors appear in low affinity when in IL2R -9. The subunit composition of IL-2RB -ILRY in the intermediate affinity. The dissociation constant of intermediated affinity IL2R is 10^-9M.

The activated CD4 and CD8 T cells contain both high-affinity and low-affinity IL2R (Hernandez et al., 2021), while the activated B cells do not (cells are in the low numbers). Resting T cells, which are in low numbers, contain the intermediate affinity IL2R. IL-2Ra is the subunit composition of low-affinity IL2R. IL-2Ra, IL-2RB, and IL-2RY make up the subunit makeup of high-affinity IL-2RY (Ayyadevara et al., 2021). It is found that low affinityIL2R can be used to sequester iron in the high-affinity receptor. The other family members of the interleukin to re-centers include IL-5, GMCSF, and high-affinity receptors alpha and beta IL2R- a, b in the high-affinity receptors. The general function of the IL-2R are neutrophil, proliferation, its SC

differentiation and proliferation, basophil degranulation, and finally, megakaryocyte and monocyte differentiation for modulating the growth and the activation during the inflammatory as well as immune responses (Borlongan et al., 2021).

1.3.3 IFN-λ, IFN-α roles in cancer immunotherapy

The Interferon-lambda (IFN-λ) is a recent type of IFN that are related to IFN-α which is usually used for the cancer immunotherapy treatment. However, the current landscape of using IFN-α in oncology is progressively increasing. The IFN-λ offers unique advantages, including a more tumor cell selective targeting, lower off-target binding and an ability to generate both innate and adaptive immune responses (Baker.et al, 2009). IFN-λ has also demonstrated therapeutic benefit in cancer therapy. IFN-λ can be used as a single agent or in combination with other immunotherapy agents, such as Immune checkpoint inhibitors, Adaptive T cell (Houston, 2019). The interferon is composed of three family classes: interferon class 1, class ll, and class lll (Tan et al., 2021). The interferon class 1 is composed of 1FN-9 1FN-B (Soday et al., 2019). Interferon class II include 1FN-Y (Loda, 2017) and IL-10(Fathy et al., 2019). Interferon class III is composed of 1FN lambda (Read et al., 2019).1FN-9, 1FN-B help in T helper differentiation out as an alarming signal. The cell signals the interferon, thereby playing an essential role against viral protection in which cell is killed by CD8 positive cell. 1FN-Y has a signal role against virus protection. When a cell is killed by a CD8 positive cell are cells that secrete some molecules, some molecules which turn to be interferon that is secreted from a viral secreted cell (Kim et al., 2018). The interferon throws the receptor signals the nuclear to produce antiviral molecules which protect the neighboring cell from further viral infection (Wang et al., 2017). One of the molecules is synthesized. The antivirus molecules produced by the interferon are the molecules that are produced as a result of signaling its protein kinase K (PKR), which binds to viral DSRNA translation or PKR (Zerbe & Cole, 2020)). The PKR causes the initiation of E1F29. The second strategy is the initiation of 2S Oligo and synthase, which binds with viral DSRNA and makes it degraded by an RNase activity. So that mRNA gets degraded and no viral protein is formed. The third strategy involves the polymerization of MX protein which inhibits the viral assembly process (Shydlovskyi et al., 2017); therefore, life process of the viral would be interfered with by the interferon. Chemokines form the next family (Miller & Mayo, 2017)). Chemokines are chemical messengers, and they form the chemical gradient (Legler, &Thelen, 2018)). The chemokines are secreted by several cells, the chemokines create gradient of high to low so that when infection occurs, so any specific molecules would easily identify from where there is a high chemokine gradient so that the immune can quickly move to the infected region. Through

the gradient creation of molecules, the immune can quickly identify the part which has been infected as a result molecule move from low to high chemokine gradient. In short, chemokine helps in its immune cell molecules navigation to the affected tumor cells. The chemokine surface expression of the adhesive molecules to the surface of the mesophyll and capillary epithelial cells of the blood vessels creating a high gradient (Mancini et al., 2018). The adhesive molecules created by the chemokine help the immune molecules identify the pathogen-infected region or cancer. The chemokine receptors are protein receptors and can work in multiple signaling pathways. The chemokine has the potential to activate the signaling pathways which regulate growth and cell division. The chemokine activates RAS (Lin et al 2018), which activates the MEKL /2/MAPK signaling pathways and activates MTORC signaling pathways (Ferreira-Marques et al., 20187). All the activation work on the AP-1 family factors which give rise to proliferous genes such as CMIC and APIM-peptide such as BCL2, due to the fact that chemokine helps in cell migration, a high gradient difference is essential. The chemokines signals lead for propagation, migration of cell, along with differentiation of the cell. (Liu et al., 2018). The Tumor Necrosis family has TNF-9 and TNF, Beta (Rohde et al., 2018); The TNF family are apoptotic but can give rise to survival alternatives. For instance, TNF-q and TNF- are secreted from macrophages, giving rise to inflammatory signals such as BAFF and APRIL leads the ultimate character for the t-cell development. FASL has great role for killing the target cell (Rossin et al., 2017). Therefore the combination strategy of IFN-λ, IFN-α can represent a better cost effective treatment for cancer patients (Satoskar; et.al; 2020).

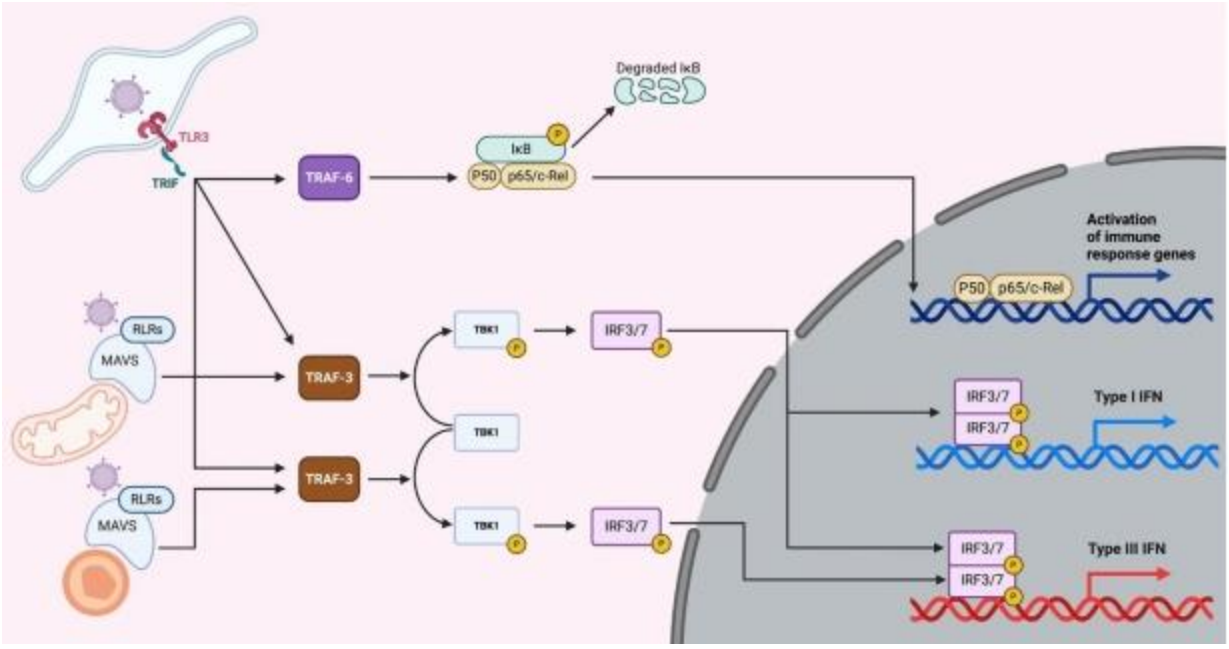

Fig: 2.1 illustrates the overview of IFN production upon viral infection. (Immunol; December 2020)

The TNF-alpha family receptor binds with the Tumor necrosis factor (TNF). Additionally, the TNF has a cytoplasmic domain known as the death domain. TRADO is a molecular factor that has a dead domain (Beyer et al., 2019). The TRADD domain (Peng et al., 2018) make a domain where other molecules can interact with the interaction of TRAF2 and activate FADD molecule (Miao et al., 2020). FADD converts the procaspase 8 to active caspase8 once the procaspase 8 is inactive to form (Hillert-Richter et al., 2021). It can give rise to the apoptosis process, which results in the death of the cell for instance killing the cells that give rise to cancer infection. In other circumstances, the TRAF2 interact with the TNF receptors death domain, when CIAP 1 and CIAP2 (Morón- Calvente et al., 2018) binds to the LUBAK, it allows the falling of ub, which refreeze TAB1 (TGF-β- activated protein kinase1) and TAB2 (TGF-β- activated protein kinase 2) from (TAK) β TGF-β-activated the kinase (Abdullah et al., 2018). Once transforming the growth factor-β TGF-β-activated the kinase 1(TAK1), it gives rise to the creation of NF-KB pathway which can make NF-KB and MADK that will migrate to the nucleus (Min et al., 2018). Once the NF-KB and MADK have been activated, it promotes the activation of the production of CFLIP that act as a tumor suppressor as well as it can stimulate the immune-mediated destruction of pre-malignant and malignant cells.

1.4 Aim of the study

Cancer is a dreadful disease causing millions of deaths every year worldwide. Among numerous treatment options for cancer, immunotherapy is the one that deals with identifying the treatment of diseases by inducing, enhancing, or suppressing the immune response of an individual (Guedes,et al; 2016). Thus, the therapies enhancing an individual's immune response are called activating immunotherapies, while the ones suppressing the immune response are called suppressive immunotherapies (Baylin,S.B;et al; 2020).

The objective of this study is to review the current concept of immunotherapy to treat cancer which includes immune checkpoint blockade, therapeutic vaccines, adoptive cell transfer therapy, and cytokine therapy are highly beneficial. Understanding how the epigenetic and mutational landscape of developing cancers is affected by the tumor-intrinsic factors and the tumoral response to immune therapies are going to be of great advantage. This project will also focus on the geographical significance and trends of immune oncology therapeutic strategies, the comparison between the general cancer treatment such as surgery, chemotherapy, and radiotherapy and IO- Immuno oncology therapy.

Chapter 2

Research Methodology

2.1 Introduction to different immuno oncology treatment

Various techniques including adoptive t-cell therapy, immune checkpoint blockade and monoclonal antibodies have been used to treat various types of cancer. They include adaptive t-cell transfer, also known as t-cell therapies, immune checkpoints that can act as inhibitors, monoclonal antibodies, on-specific stimulation, oncolytic virus's immune therapy, and vaccinations. Each technique is distinct from the others. Among the immuno oncology treatment strategies the Checkpoint inhibitors are the extensively used immunotherapies for advanced cancer treatment though Checkpoint blockade has shown relatively low response rate having some major side effects. Checkpoint inhibitors target to reactivate exhausted or suppressed T cells in the tumor environment (TME) (Lu R.M. 2020). On the other hand, Monoclonal antibody therapy is also an established techniques based on the cloning of synthetic DNA sequences. In case of T-cell therapy it is a type of treatment where a patient's T cells known as a type of immune cells are changed in the lab so that it will bind to cancer cells and enable to kill them (Lenardo,et.al 2020). For vaccination therapy it has emerged as a fascinating immunotherapeutic approaches against cancer because of its stability, safety properties. In addition to, vaccination therapy has shown a less side effects and cost effective characteristics (Jeang, et al; 2014).

2.1.1 Adoptive t-cell immuno therapy for cancer

For harnessing the immune system and for identifying or to demolish the tumor cells Adaptive T cell have a certain aim for anti-cancer treatment. In recent times, the main treatment modalities within cancer immunotherapy has been adoptive T cell therapy (ACT) (Varela; et.al; 2018). Moreover using this approach, tumor-specific cytotoxic T cells are infused into the cancer patients for recognizing, targeting, and destroying the tumor cells. Peptide epitopes can be identified along with the lymphocytes t-cell. These type of cells are derived from antigen-containing tumor cells. Furthermore, T cell receptors that identify peptide epitopes can be programmed into autologous CD8+T cells generated from the patient. T cell therapy using CD 8+ T cells can kill the eruption or tumor cell such as an epitopes utmost class 1 molecular immunizing agent compound, according to (Rosenberg and Restifo, 2015). Finding a proper epitope selection is crucial to building a successful adoptive T cell therapy. In melanoma

patients, ACT treatments have been found to be successful by inhibiting immunological identification of cancer cells, resulting in immune escape (Chandran et al., 2014). Melanosome proteins are the most prevalent melanocyte differentiation antigens. Melanomas use inflammation-induced differentiation to stop MDA-directed ACT (Landsberg et al., 2012). Melanoma cells have the ability to suppress non-essential MDA expression. Tran et al., 2016; Anders et al., 2011). This could help the target's chances. The epitopes from expressed genes are also more likely to survive in cells. The schematics below show a CRISPR-Cas9-based (Crispi tope) strategy for binding model of CD8+ T-cell epitopes of diverse internal gene substances in malignant cells. The immunogenic (epitope-tagged) allele was silenced selectively, highlighting the significance of regulations to oncogenic into the potential antigen. In addition, ACT immune escape strategies, the function of the gene substances cab be produced tumor-specific T cell target epitopes are also crucial.

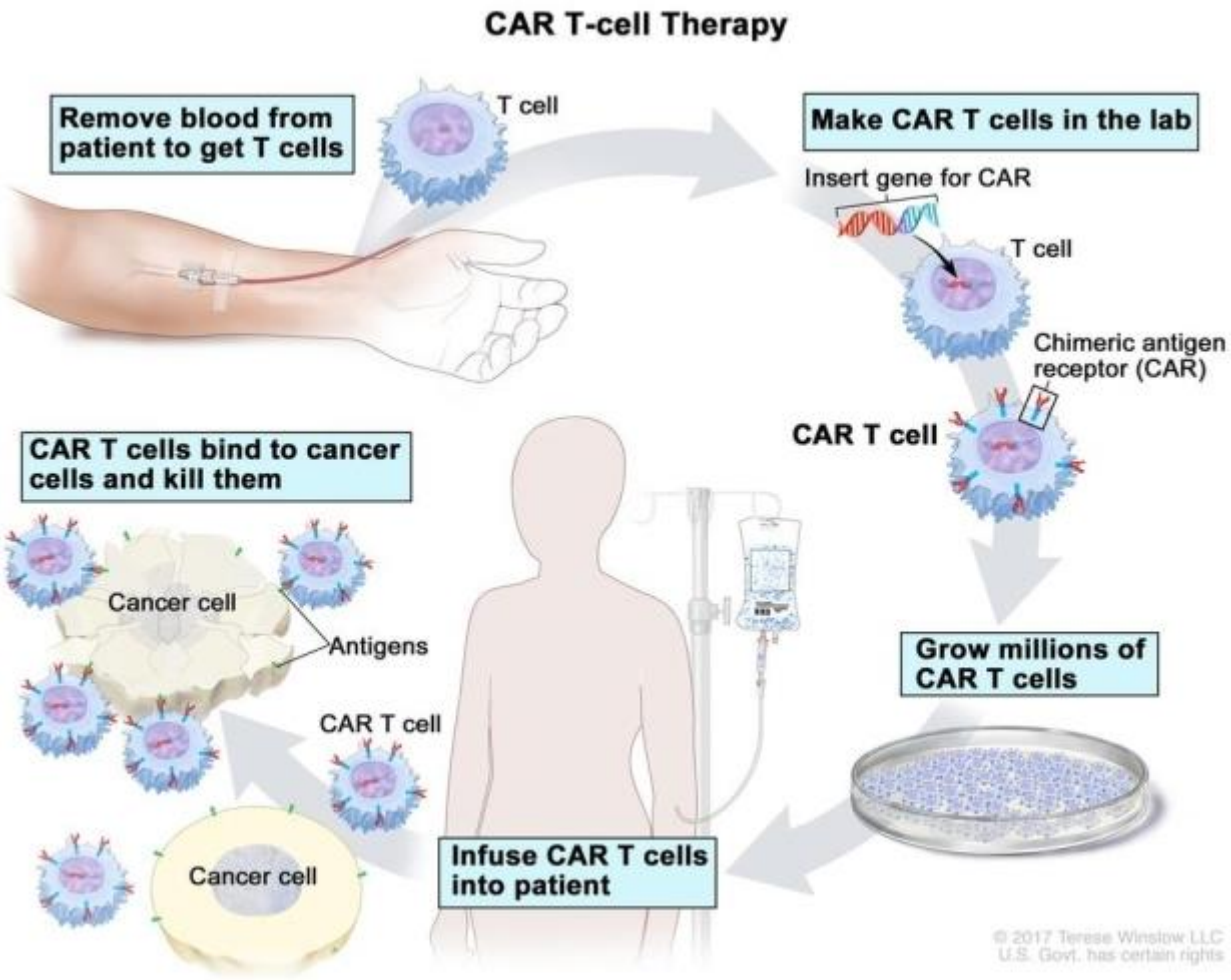

Fig 2.1.1: The figure shows the T-cell therapy mechanism. (Reuse of NCI Information; February 2022)

2.1.2 Immune checkpoint inhibitors therapy for cancer

Immune checkpoint blockade is a type of immunotherapy for cancer treatment. In immune checkpoint inhibitors drugs block several checkpoint proteins such as CTLA-4 blockade, PD-1 inhibitor as well as PD-L1 inhibitor. There have also immune Checkpoint inhibitors includes pembrolizumab, ipilimumab, nivolumab (Haanen, et al; 2017). The field of immunooncology has been fundamentally transformed by immune checkpoint inhibitors (Takayma, et al 2020). The immune checkpoint inhibitor can select cytotoxic and also an antigen termed T lymphocytes that is the initial one to be accepted as the treatment of metastatic melanoma patients. It acts by altering co-barrier signal path also promoting tumor cell detect and eliminate via the immune system (Zielinski; et.al, 2017). It inhibits T cells while increasing the promptness along with multiplication of effector T cells. Despite to success, only a subset of patients have benefited

from ICIs to generate variable immune responses, antitumor immune responses may be regulated by complex factors in the tumor environment, and some patients experience severe side effects after undergoing ICI therapy (Hu-Lieskovan, et al; 2019).

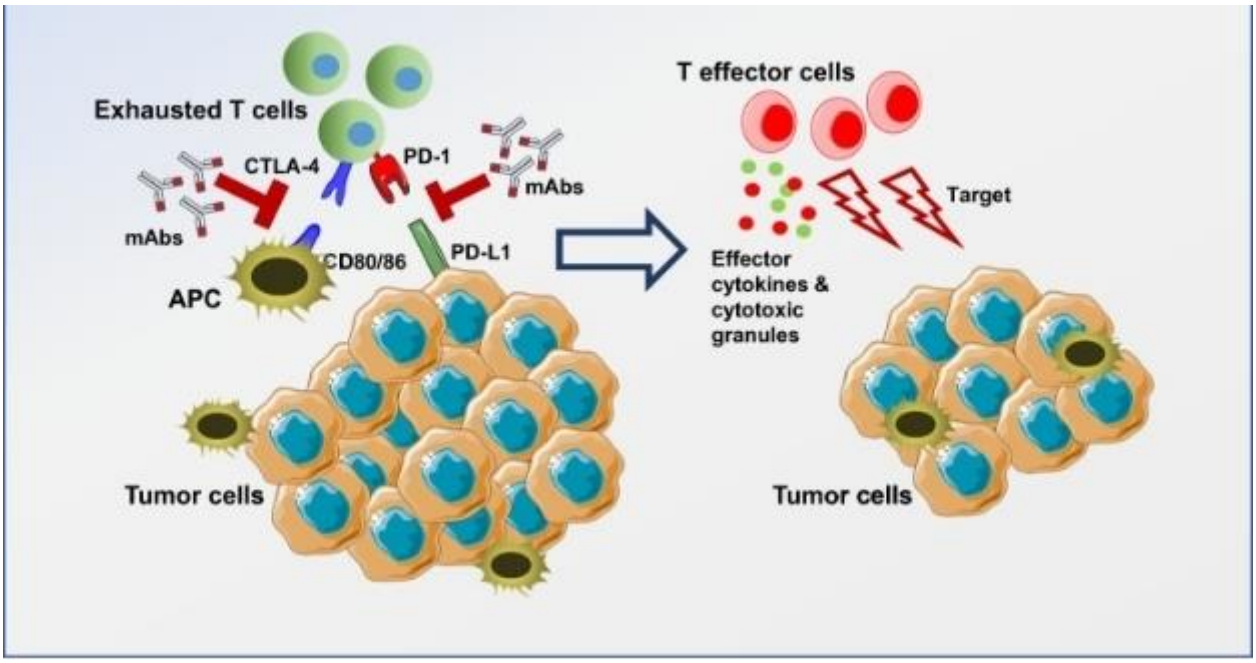

Fig: 2.1.2 Checkpoint blockade for T-cell activation (Darvin, Toor, Elkord; December 2018).

When immune checkpoints produced by activated of the PD-1 and CTLA known as t-cell, connect with the cell that present antigens or else tumor cell, they may inhibit T-cell activation (Keisuke, et al; (2018). T lymphocytes can be stimulated by monoclonal antibodies, which then release such effector containing granules of the cytokines as well as cytotoxic to attack tumor cell. Immune checkpoint inhibitors have different effects based on the TME (D. Schoenfeld, et al; 2017). The tumors of responders contain a high neoantigen burden, a large number of the TILs, particularly the cells of effector, containing a large number of Teff to Treg ratio, less MDSC amount, and enhanced the release of IFN, or another cytokine release. Non-responders' TME hold a massive proportion of immunosuppressed cell called Tregs, MDSCs, as well as a low proportion of NK cells and activated lymphocytes (Elkord, 2019).

2.1.3 Monoclonal antibodies therapy for cancer treatment

Monoclonal antibody therapy based immunotherapy is now considered as a key components for cancer therapy, along with surgery, radiation, and chemotherapy. Monoclonal antibodies possess a different set of clinically relevant mechanisms of action. In addition to, antibodies can target directly the tumor cells while simultaneously promote the induction of long-lasting anti-tumor immune responses (Weiner; 2020). Antibodies such as monoclonal (mAbs) can be produced from a single B-cell through clones of a single B cell that individually bind to a distinct epitope on an antigen (Ferrone; 2016). Antibodies are also capable to target certain tumor cells. T-targeted mAbs can kill tumor cells in different ways by targeting tumor-specific or overexpressed antigens (Fig 1). However, the targeted Monoclonal antibodies (mAbs) acts against antigens. It can either identical or to be overexpressed by tumor cells that can cause tumor cell death. One of the main direct mechanism by which most of the antibodies can induce tumor cell death is the blockade of growth factor receptor signaling. The pro-tumor growth signaling is perturbed when mAbs bind to the target growth factor receptors and manipulate the activation stages or block ligand binding (Weiner; 2020).

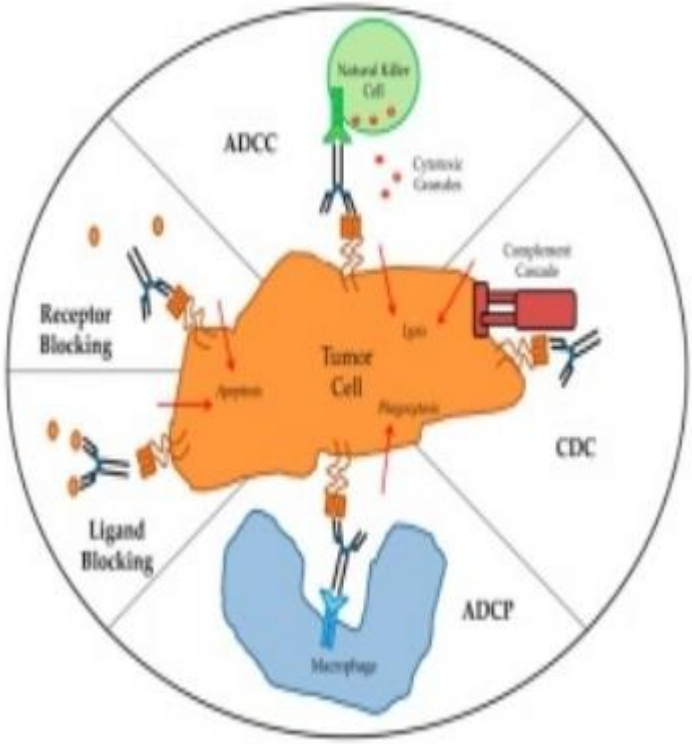

Fig: 2.1. 3 The diagram depicts the mechanisms of antibody effector (Zahavi; et al; 2020).

Oncolytic virotherapy is a new modality for cancer treatment which uses for the component replications to demolish cancer cell. Oncolytic viruses are weakened viruses it can be infected tumor cells also elicit new immune responses while also strengthening pre-existing immune responses on the local level (Gopisankar, 2018). The bulk of oncolytic viruses on the market have their virulence in non-neoplastic host cells that can reduce while improving the tumor tropism. As a result, by promoting the pro-inflammatory milieu, they can increase releases of antigen detection and activation of the subsequent immune system to fight malignant immune cell evasion (Jian Ma, et al 2020). In reality, oncolytic viruses strive to exploit the tumor's tolerogenic pathways, which enable viral infection and killing of immune-compromised cells. This could set off a chain reaction of viral transmission and immunological activation in cancer cells. Meanwhile, oncolytic virus-based immunotherapies contains the action of multimodal mechanism that includes autolysis, immune cell sharpening, supply of vascular disruption, also enhancing the other therapies of anti-cancer (Rutka, et al; 2016). There are host factors that predict the success rate of oncoviral therapy. Prior to inoculation, the tumor presence of penetrating lymphocytes and massive tumor appearance of immunomodulation can target the most positive portend of the immunotherapeutic responses for both models such as human and animal. Among these, most important marker associated with immune-stimulatory agent sensitivity has been identified as upregulation of type I IFN. Oncolytic viruses can also influences by acting as a therapeutic adjuvant (Melcher, 2021). Herein, within four more than one of it can be in the percentage of twenty five percentage (25%), individuals by melanoma. It initially do respond to the PD-1 axis blocking acquire confrontation, using PD-1 axis inhibition as an example (Zhang 2020).

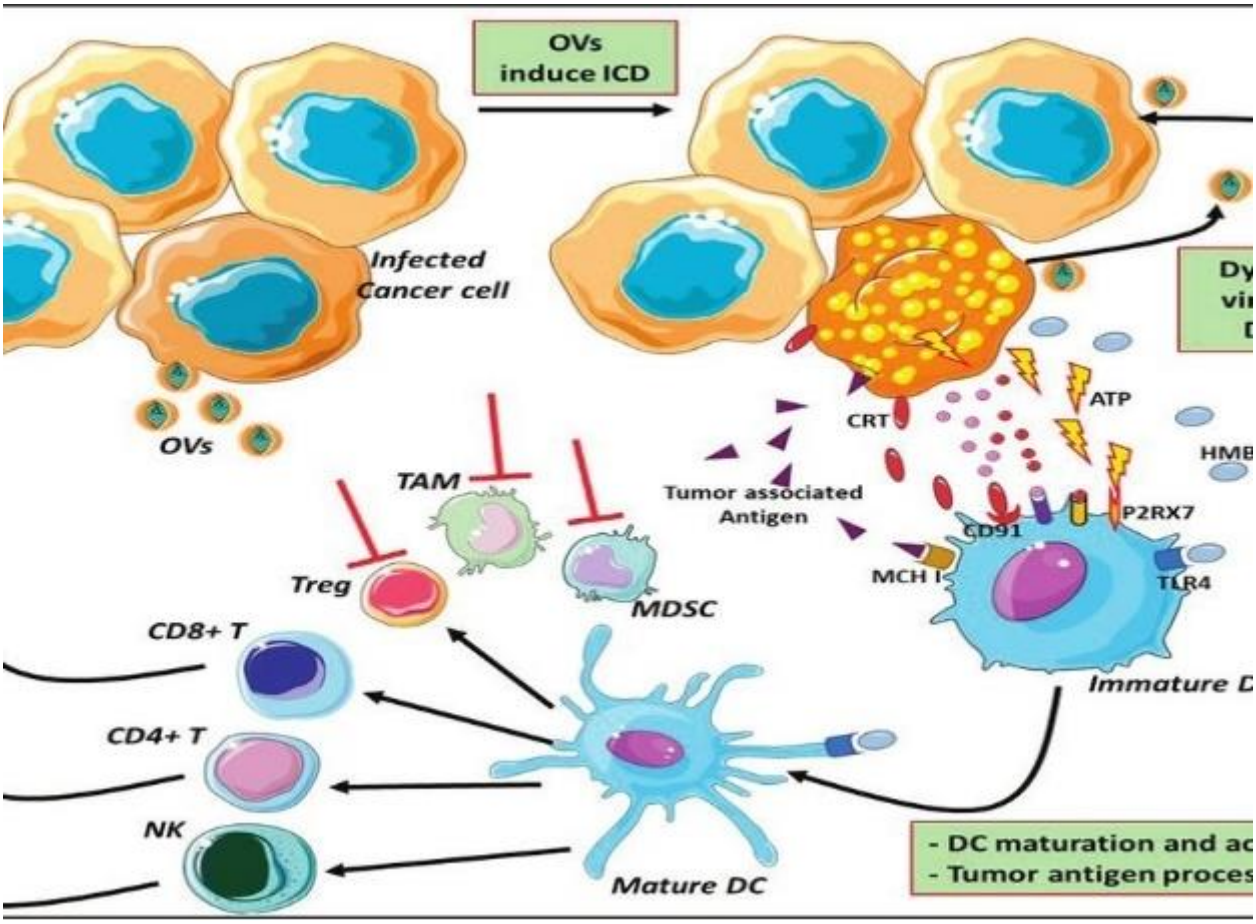

Fig 2.1.3.1: The figure illustrates the oncolytic virus mechanisms (Martini; et al, 2020).

2.1.4 Vaccinations therapy for cancer treatment

Combinations of recombinant antigen, microorganisms that are recombinant and complete the cell of tumor resulting allogeneic, oncoviral or oncolytic viruses and antibodies are examples of off-the-shelf cancer therapeutic vaccines (Rafati, 2011). Cancer vaccines known personalized vaccines (antigens or cells of autologous, adoptive cell transfer), as well as DNA and therapy-based on gene therapies that might be developed and distributed globally (Garcia, 2013). Dendron's Provenge (sipuleucel-T), dendritic cell vaccines for metastatic cancer castration-resistant prostate is the sole vaccines authorized by the FDA in 2010. Despite considerable preceding attempts and trials. For the cancer vaccines (CVs) are an extended-desired healing or preventive immunotherapy tactic for eliciting antigen (Ag) - explicit T-cell responses and possibly achieving enduring clinical advantage. Nonetheless, despite promising signs of immunogenicity, furthermost CV clinical studies have historically yielded impermissible results (Saxsena, 2018). There have two basic approaches includes physical delivery to acquire the

higher level of antigen production and the formulation with small particles to target antigen-presenting cells (APCs) has shown the effectiveness for immuno oncology therapy. New developments in vaccine delivery systems may improve the efficiency of clinical studies in the near future (Bolhassani; 2017).

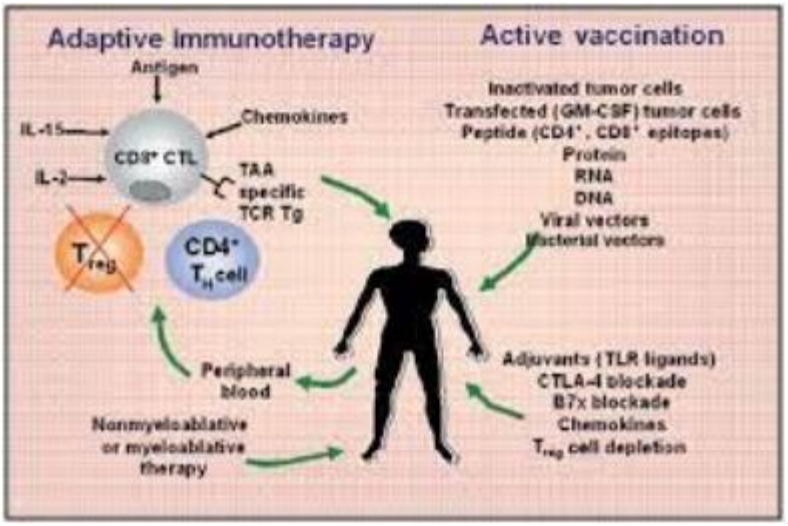

Fig: 2.1.4 illustrates the cancer vaccines mechanisms (Pure; et al 2006).

Chapter 3

Geographical Significance and Trends of Implementation of Immune-oncology Therapeutic Strategies

3.1 Implementation of cancer immune therapy treatment

Using immuno-oncology (I-O) as a treatment for various forms of cancer is a novel and cutting-edge approach. Over the last few decades, it's been proven to work. However, I-O treatments make the body's defenses work harder to locate and remove the growth, which would otherwise go unnoticed by the immune system. However, even though there are just a few approved I-O therapies, they are already making a difference in treating some tumors. It wasn't long before new treatments improved due to this subject becoming more widely discussed. This demonstrates the importance of the field and how the subsequent well-known treatment, I-O, may be utilized to treat cancer (Kamta, 2017). In many studies it illustrates that the immune system can locate and eliminate tumour cells after studying animals and then on people. Oncologists have been studying the immune system to understand better when and why cancer immunotherapy and tumour rejection do not function in patients. Immunotherapy is a form of treatment to support the immune system, detect tumours and restore the immune effector function that has been damaged (Finn, O. J. 2012). Because of rapid growth in immuno-oncology (I-O) therapy, patients with multiple forms of cancer and advanced tumours now have superior long-term survival rates. A better grasp of the treatment's many features and properties and a better grasp of how patients view these therapies will aid in these evaluations. In this research, I-O therapy stands out from the competition. This report also provides valuable information for evaluating the value of I-O treatments and attempts to fill in data gaps within the present value framework because of the unique clinical outcomes associated with I-O therapy. As a result of gaining a greater understanding of the benefits of I-O treatments, a framework for the design and ranking of clinical studies will be established, and guidelines for public health care insurers on how to best serve patients with I-O-treatable cancers (Kaufman H. et al., 2019).

3.2 Comparison with general cancer therapies

Compared to other cancer treatments, I-O therapy may be more effective for certain patients with certain forms of cancer. Instead of targeting the tumour directly, I-O treatments rely on the immune system to identify and eliminate malignant cells. Immunotherapy relies on sensitivity, response variety and long-term memory all of which are critical aspects of treatment (Mazouz, 2015). In contrast to cytotoxic chemotherapy, molecularly targeted medicines and radiotherapy can induce tumours to shrink completely, improving long-term medical results and quality of life for patients with severe illnesses kinematics and characteristics of immunotherapy impact side effects, treatment duration and response stability (Riwanew, et al., 2019). A few people remain skeptical despite numerous cancers being approved by the Food and Drug Administration for I-O therapy. Malignant tumours, kidney, bladder, lung, and head and neck cancers are only a few more common types. There are many different types of cancer, including Merkel Cell and Hodgkin lymphoma, non-Hodgkin lymphoma, some kinds of leukemia and primary, site-independent tumours. The differences must be taken into consideration (Kaufman, et al., 2017).

3.3 Compare and contrast between immuno oncology studies

Table1: Different studies conducted on geographical trends of implementation of Immuno-oncology therapeutic strategies

Sr. No	**Title of Research**	**Immuno-Oncology technique used**	**Geographical area of study**	**Results**	**Limitations**
1.	Brazil's access to immuno-oncology therapies is being expanded. (Santos,2019)	Use of cost-effective drugs as immuno-oncologic therapeutic strategy	BRAZIL	This research provides a set of guidelines that are likely to improve access to these critical treatments while also lowering their costs. However, community is to profit from this	No other immune-oncology techniques are compared to give effective results in terms

				tremendous progress in health care, significant difficulties must be solved.	of implementation.
2.	In China, immuno-oncology is advancing clinically. (Yang, et al., 2020)inically	Analysis Implementation of immuno-oncology drug for last 5 years	CHINA	The advancements in oncology immunotherapies in China prompted us to investigate into the data on the prognosis and evolution of these treatments in China, that can help industry, governments, and other stakeholders set future goals.	In terms of application, no other immune-oncology strategies are considered to provide effective results.
3.	The development and future promise of a tailored immuno-oncology therapy for a number of tumor types using the BiTE (bispecific T-cell engager) platform. (Berghaus, et al.,2020)	BiTE (bispecific T-cell engager) used as immune-oncological therapeutic treatment for different tumor types	Germany	By eradicating MRD, BiTE treatments have the capability to improve deep and long-lasting effects. The adoption of blinatumomab and the upcoming clinical evidence from BITE pipeline medicines demonstrate the platform's ability to make significant oncology advancements.	Not a cost-effective method Some other types of cancer patients such as breast cancer do not show much higher response rate

4.	In the Middle East, this is the first advanced course on biomarkers in molecular and immuno-oncology (Moujaess, et al.,2021)	Implementation of molecular biomarker implementation for immuno-oncology therapeutic strategy	Middle East	A Report based on conference which invited Researchers to discuss innovations related to molecular biomarkers as immune-oncologic strategies.	That was not proper study
5.	A positive experience in Bangladesh with ivermectin and doxycycline in cancer patients with COVID-19. (Shuayb,2020)	Ivermectin and doxycycline oncological drugs used to treat COVID-19 impacted patients.	Bangladesh	These initial results could serve as a foundation for larger-scale investigations in the future, and randomized controlled trials involving only people with cancer are needed to confirm the therapy's effectiveness.	This study did not compare these drugs against other molecular strategies used for rehabilitation of immunity in cancer patients

3.4 Difference between different immuno-oncological therapeutic techniques

3.4.1 Adaptive t-cell therapy

T-cell adaptive therapy is a type of immunotherapy that can use body's own immune cell and make it able to attack cancerous cells. There are two types of T-cell transfer therapy: tumor-infiltrating lymphocytes (TIL) therapy and CAR T-cell therapy. Chronic inflammation may be the root cause of the wide range of cytotoxic T-cells that develop, which can lead to devastating malignancies. As a result, the T-cell antigen receptors were stimulated for an extended period. This may be due to an increase in inhibitory receptors and a decrease in T-cell effector activity. (Minnie, et al., 2018). However, there is no data to suggest that CD8+ T-cells are reduced or die off in patients with multiple myeloma (MM) who have T-cell exhaustion (Minnie, et al., 2019). In multiple myeloma patients, T-cells in the bone marrow (BM) were more damaged than in the peripheral blood from the periphery (PB) (Dumeaux, 2016). Near the tumour site, CD8+ T-cells revealed numerous signs of T-cell exhaustion, as well as PD1 and CTLA-4 (BM). Because of the importance of using checkpoint inhibitors before in MM to prevent T-cell depletion and provide long-term autoimmune control, IL-10 processing and the t-cells immunoglobin and immunoreceptor tyrosine-based inhibitors (ITIM) called motif domains (TIGIT), and PD1 expression were the primary reasons (Zelle-Rieser C et al., 2016).

3.4.2 Immune checkpoint inhibitors

When both co-stimulation and co-inhibition immunological checkpoints are turned on the immune system works together to protect the host from autoimmune and inflammation-related damage (Badros.et al. 2015). Tumour are supposed to get around the immune system by increasing molecules that make T-cells less active. An immune checkpoint inhibitor was used to stop T-cells from making the receptors that block them completely reverse in this state. It can stimulate person's immune system taking them, which has an anti-tumour effect. People with multiple myeloma were given antibodies as PD-1 blockers (Pembrolizumab and Nivolumab) and PD-L1 blockers (Durvalumab). Most likely, this is because they cannot respond to monotherapy, which is why they have a terrible immune system (Suen H et al., 2015).The CTLA4 and PDL-1 alignment has been shown to work in many different types of cancers both solid and hematological. It is also one of the most critical medical inhibitors so far. Because immunomodulatory drugs (IMiDs) may be able to stimulate both adaptive and innate immune

systems simultaneously, better results have been seen when they are used together. However, those interactions led to side effects (AEs), including lung, heart, intestinal, and liver toxicity and a higher risk of death. This led to safety issues. There is still a chance that immunotherapeutic inhibitors could be a promising treatment for people with multiple myeloma, but more research is needed to improve clinical efficacy and reduce immune-mediated toxicity (Jing W et al., 2015).

3.4.3 Monoclonal antibodies

Two decades of research have proved that monoclonal antibodies are one of the best cancer treatments for both hematological and solid tumours. Clinical trials combining immunohistochemistry and serology paved the door for developing novel antibodies and treatments. Fc modifications have also improved cancer treatment by altering the immune system's ability to combat the disease. Changing the immune system's interaction with tumour cells by attacking T cell receptors appears to be a promising new approach to cancer treatment and vaccine development (A. M. Scott, et al., 2012). Researchers discovered that immune-senescence was the cell's most prevalent trait. Because of the presence of positive killing cell lectins like receptors, they can determine that the T-cells were in a dormant secretion effector state. There is a biochemical marker of maturation, not depletion, in multiple myeloma (MM) T-cells. To assist the body produce new immune cells capable of fighting off the antigen, antibody treatments may be used. An antibody that recognizes an antigen may aid in producing new immune cells to combat it. Thus, new immune responses may begin to build, allowing antigen-specific antibodies to continue to have an impact even after they have been administered (Suen H et al., 2015).

3.4.4 Vaccination

Using tumour markers in anti-cancer vaccinations can help to boost the immune system and make it enable to fight with cancer. Many preclinical and clinical studies have been conducted using these distinct therapies to diagnose cancer as lacking in enthusiasm. Several medicinal vaccinations have been developed so far. Antigen-modified DNA, RNA, and viral vectors could also create peptide and vaccination antigens. When the tumour burden is modest, treatments such as stem cell transplantation (SCT), smoldering or myeloma (SMM), and MRD implantation have

all been employed in MM multiple myeloma (Cohen AD, 2019). Cell-based vaccinations are investigating the use of allogeneic DCs (Dendritic cell) with high concentrations of tumour antigens. As a result, in phase II of the study, MM patients were given a hybrid vaccine created from autologous MM and DCs after having an ASCT procedure. Fusion vaccines and anti-PD-1 medication are helping patients in clinical trials. These vaccines appear to be well stablished and it is widely accepted that they perform best when taken in conjunction with other immunomodulatory medications. MM may benefit from vaccinations, which may increase the likelihood that the treatment will work or last longer (Rapoport, et al., 2015). In cancer immunotherapies, finding medications that perform well for most individuals and cancer types is a significant challenge. Some cancer immunotherapy patients have achieved tremendous benefits indicating that their immune systems can function normally again. People's responses to cancer immunotherapies vary widely for a variety of reasons (Mougel, 2019). A vast range of cancer types and stages, treatment history, and cancer immunosuppressive biology are just a few of the issues that need to be addressed. Minor improvements in cancer survival have been made by treatments that focus on a single genetic mutation or disease pathway. Drugs that target many mutations and cancer pathways can be given concurrently in this technique. Mutations identified in human cancer cells aren't always detected in the same manner across patients. Immunotherapies that target genetic alterations will almost certainly need to be customized for each patient to be effective (Guo, et al., 2016). Low target selectivity, drug resistance, ineffectiveness in treating metastatic cancer, a severe side effects are all issues that persist. On the other hand, immunotherapies are showing great promise in the trial, using the body's immune system to fight tumors. The body's immune system which contains natural killer (NK) and T-cells, can detect most malignant tumours. Genetic instability and other "hallmarks" that can circumvent the body's defense mechanisms are hallmarks of cancer cells. Immunity in the host has been proven to recognize "neoantigens" on tumour cells in the laboratory (Pallocca,et al 2018). Tumours in the body have a complicated microenvironment, consist of various cell types, and are constantly developing; therefore, neoantigen detection alone will not be sufficient to eradicate them. Though few people are familiar with the fact that neoantigens can elicit antitumor T-cell responses on their own.

Chapter 4

Discussion

Chapter one encompasses the literature review on immune oncology and how the immune systems help to treat cancer. The objective of this chapter is to provide thorough and comprehensive knowledge on this topic in terms of cancer cell treatment. This chapter highlights the following aspects different types of tumor antigens, specific and non-specific one. In contrast, chapter one also provides the stages that contains the growth and development. Furthermore, the requirement or the formation of interaction of immune system, roles of cytokines and general function of interleukin inflammation also have been briefly discussed.

Chapter two introduced the different technique that are related to treat cancer cells in our body. This chapter illustrates some advanced treatments that employ body's particular immune system to combat cancer. They are adoptive T-cell therapy where metastasis limits durable for cell therapy that can recognize certain peptide epitopes. Secondly, Immune Checkpoint inhibitors are discussed here using some different mechanisms by which tumor cells can evade the immune surveillance and progress. In the field of immune oncology are a revolutionary milestone. Another technique is monoclonal antibodies, which have a significant set of clinically relevant mechanisms. For promoting the long established of antitumor immune response induction antibodies are being able to target cells that are causing tumor.

Chapter three illustrates the advanced therapeutic strategy such as Immuno-oncology (I-O) therapy. I-O treatments, can specifically attack abnormal cells, activate the body's certain immune systems and destroy the tumor cells. In different regions it shows different geographical trends for example, in case of China, from last 5 years they are analyzing for implementing the data for immuno-oncology drugs. Moreover, Germany is known as an advanced country in case of cancer treatment they are already eradicating MRD and others treatment process for improving the immuneoncology treatment sectors. For the Middle East country, Researchers do discuss to innovate related to molecular biomarkers for treating immune oncology therapy. Lastly, in Bangladesh a positive result has been experienced with ivermectin and doxycycline in cancer patients. Chapter three also represents the several

immunooncological therapeutic strategies including T-cell therapy, Monoclonal antibody, Vaccination therapy and Immune checkpoint blockade.

It is assumed that using a variety of data sets improve the accuracy of the results and open the study up to multiple interpretations. Furthermore, this study could have a substantial influence on the public health sector in the near future. Finally, this review paper may help to put the global perspective of imuunooncological shifts for practice in Bangladeshi patients in the future.

Chapter 5

Conclusion and Future Directions

Over the last few decades, numerous researches have uncovered new knowledge on the relation amongst cancer with the immune systems. In modern era, the success rate for the cancer immunotherapy has risen considerably. However, there are still challenges to be overcome in the sector of medicine. Combination therapies that is personalized are cutting-edge methodologies that could be used in the next generation of cancer immuno-oncology treatments. In this study, we presented the future vision for the next generation of treatment strategies, which includes mAbs that is monoclonal antibodies, vaccination for cancer therapy, adoptive cancer therapy, as well as immunological checkpoints. In this field of therapy, it has progressed significantly. (2018) (Source: Zhang et al.)

As reported by the American Cancer Society, the quicker exploration of immuno-oncology (I-O) therapies for a broad range of tumor types has revolutionized the world of cancer treatment and managed to improve the long-term prognosis for so many patients with advanced disease, regardless of the fact that it has only taken a short period of time. In response to the growing efforts to just provide value assessments for new treatment strategies. A complete assessment is needed so far for the features and attributes of these treatments as well as to get a better knowledge of how these therapies effect patients. This study discusses the contrasts between I-O treatment and conventional therapies, as well as the similarities and differences between the two. Important characteristics and qualities of I-O treatments are also discussed. It also included the recommendations for closing evidence gaps in current value frameworks, which is necessary given the unique characteristics of patient outcomes associated with I-O therapy, as well as recommendations for bridging evidence gaps in current value frameworks. I-O therapies are not routinely and robustly measured in existing clinical practice and reimbursement databases, nor do they appear to be consistently captured by existing research studies, as is the case with current clinical practice and reimbursement databases. For cancer patients who are appropriate for I-O therapy, it will also be conceivable to much more accurately quantify overall effectiveness of the treatment, and this information will serve as a template for the design and prioritization of future

clinical studies. Cancer patients who are eligible for I-O treatment will profit from it as well as healthcare insurers who will gain from having a roadmap to maximize coverage for these patients.

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