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Immunotherapy toxicity - An overview

Presented by: Abbas Soumaya & Kouider Marwa

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Dedication

I dedicate this humble piece To my father, who has been my shadow and supported me throughout all the years of studies, who ensured to assist me, inspire me, safeguard me, and being a good listener.
To the one who gave me life, who accompanied me with prayer, encouraging, hopeful, and faith in me, to my mother.
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Without forgetting my companion Soumaya, my best girl since high school , I appreciate your endurance and being patient with me, so I can't tell nothing more than a heartfelt and genuine thanks for being there for me.

MARWA

Dedication

In the name of Allah, and prayers and peace be upon the Prophet of guidance To proceed: Praise be to Allah who enabled me to complete this work by His grace and presence, Glory be to Him
To the beautiful cloud that has passed away but still raining in my heart, my dear father, who would be the proudest of people, a father who is not like all fathers, may Allah have mercy on you and grant you his highest paradise.
To the affectionate embrace and the warm touch, to the one whose supplication did not leave me for a moment, my motivation to continue, my encouragement, to my precious mother, my love.
To my diamond in the rough my support in this life, my wrist that does not twist , My brothers, the joy of my eye: Youssef, Ayoub, Ibrahim and Moussa, my Allah protect you all.

To my brother's wife and all my family, young and old , near and far, to everyone who knows me and wishes me well.

To those who rejoiced at my joy and grieved at my sorrow, to those who shared with me the moments of my life, to my sisters whom my mother did not give birth to, my companions, my friends and my neighbors, in residence.

Without forgetting my bestie whom I cannot describe and my partner in graduation Marwa, I ask Allah to help us and all our colleagues in the field of toxicology, room 306

SOUMAYA

Matriarch's table

List of abbreviations

ACEI : angiotensin converting enzyme inhibitor

ACT : adoptive cellular therapy

ADCC: antibody dependent cellular cytotoxicity

ADCP : antibody dependent cellular phagocytosis

ADEM: acute demyelinating encephalomyelitis

AE : adverse events

AIDP: Acute inflammatory demyelinating polyneuropathy

AIN : acute intestinal nephritis

AKI :acute kidney injury

APC : antigen presenting cells

ARDS : Acute respiratory distress syndrome

ATG: anti-thymocyte globulin

ATIN: Acute tubulointerstitial nephritis

BOOP : bronchiolitis obliterans organizing pneumonia

CAR-NK : chimeric antigen receptor-modified natural killer

CAR-T : chimeric antigen receptor T

CDC: complement-dependent cytotoxicity

CEA : carcinoembryonic antigen

CIDP : chronic inflammatory demyelinating polyneuropathy

CIK: cytokine activation killer

CK : creating kinase

CLS: capillary leak syndrome

CMV: Cytomegalovirus

CNS : central nervous system

COPD : Chronic obstructive pulmonary disease

CPI :checkpoint inhibitors

CRS: cytokines release syndrome

CTCAE : Common Terminology Criteria for Adverse Events

CTL : Cytotoxic T-lymphocyte

CTLA-4 : Cytotoxic T-lymphocyte antigen 4

DAMP : Damage-associated molecular pattern

DRESS : Drug rash with eosinophilia and systemic symptoms

EBV: *Epstein-Barr virus*

ECOG: Eastern Cooperative Oncology Group

FDG : fluorine-18 deoxyglucose

GI : gastrointestenal

HER2: Human Epidermal Growth Factor Receptor-2

HPV : Human Papillomavirus

HSV1: herpes simplex virus type 1

IBI : Immunoblockers

ICANS: immune effector cell-associated neurotoxicity syndrome

ICI: immune checkpoint inhibitors

ICU: intensive care unit

IFN-a : interferon-a

IL : interleukine

ILD : Interstitial lung disease

IR: infusion reaction

IRAE : immune related adverse effects

IVF: intravenous fluide

IVIG: intravenous immunoglobulin

LAK: lymphokine activated killer

mAb : monoclonal antibodies

MG : mysthenia gravis

MRI : Magnetic Resonance Imaging

NK : natural killer

NKT : natural killer T

NMDA : N-methyl-D-aspartate receptor

NSCLC : non-small cell lung cancer

OV : oncolytic viruses

PAMP: Pathogen-associated molecular pattern

PCR : Polymerase chain reaction

PD-1 : programmed death receptor 1

PD-L1 : programmed death receptor ligand 1

RCC : renal cell carcinoma

RRT : renal replacement therapy

SJS : Steven's Johnson syndrome

TEN : toxic epidermal necrolysis

Th1 : T helper 1

TILs : tumor-infiltrating lymphocytes

TLS : tumor lysis syndrome

TNFa : Tumor necrosis factor a

WHO : world health organization

EGFR : Epithelial Growth Factor Receptor **FDA** : food and drug administration	

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INTRODUCTION

INTRODUCTION

Cancer is a genetic disorder known as genomic instability where many point mutations build up and structural changes occur in the tumor progression process **(Zhang and Zhang, 2020)** that makes it an injurious disease and one of the most serious threats to human health even its cells develop exponentially at a very rapidly rate and propagate by escaping the immune system **(Troussel, 2021)** which makes it a complex and intelligent disease, so its treatment methods have changed significantly in recent years, from conventional surgery, chemotherapy and radiotherapeutics to the emergence of targeted therapies **(Alahmadi *et al.*, 2022)** nevertheless there are limitations to these methods, such as trauma, poor targeting, severe toxicity, and drug resistance **(Yang *et al.*, 2022)** which have led scientists around the globe to support therapies that reinforce the body's natural abilities to fight cancer through using another type of treatment that has changed the landscape of cancer therapy and one of the most promising discoveries are currently being made it's the immunotherapy **(Crichton, 2017)**.

The human immune system is responsible for recognizing oneself in relation to nonself, thus protecting the body against diseases of exogenous and endogenous origin **(Abbott and Ustoyev, 2019)**. This biotherapy involves stimulating the immune system through various treatments It is therefore necessary to awaken it in order to enable it to fight against tumor cells. It is already well-established in dealing with other diseases such as rheumatoid arthritis and allergic asthma. As a result, immunotherapy is thus viewed as a novel modality and a genuinely revolutionary approach to cancer management.

Immuno-oncology uptake is rapidly increasing in cancer treatment. Improved life expectancy and quality of life for patients with several types of cancer have led to greater use of immunotherapy and expanded classes and drugs available to oncologists **(Chhabra and Kennedy, 2021)**.

Some immunotherapeutic agents directly attack the cancer cells and prevent metastasis. Other types boost the immune system to attack cancer cells thereupon it is not a single kind of treatment, but a variety of treatments that harness the immune system's ability to combat. **(Crichton, 2017)**. It includes the use of cancer vaccination the idea behind it is conceived to trigger and magnify anti-tumor immunity, adoptive T-cell therapy (ACT) involves collecting patients' own T-cells, enhancing their *ex vivo* performance and retransmitting them **(Riera-**

Domingo *et al.*, 2020), cytokines by assisting in modulating or regulating the activity of the immune system to combat cancer, treatment of oncolytic viruses (OV) through infecting tumor cells and incorporating lasting immune responses for cancer destruction, and immune checkpoint inhibitors (ICI) by blocking the immune control point's adverse regulation over the immune response to antitumor drugs **(Yang *et al.*, 2022)**.

However, this promising treatment harnesses the body's innate immune system to target cancerous cells. It may consequently result in detrimental, even deadly, immune-related and significant inflammatory adverse effects in one or more organs **(Rahman *et al.*, 2022)**. With the spread of these drugs, clinicians need to be aware of the toxic effects associated with their use **(Chhabra and Kennedy, 2021)** Due to thier complex and variable toxicities, most are reversible and manageable, and early management will increase the patient's chances of recovery **(Alahmadi *et al.*, 2022)**.

The purpose of this documentary analysis, based on the most recent research reports, is to provide an illustration of the toxicity of immunotherapy and its side effects, moreover to suggest solutions and find out about managements and treatments for these issues. The manuscript is divided into 3 chapters, the first one represents an opening to immunotherapy Definition, History of immunotherapy, Immunoediting and Immunotherapy strategies furthermore, the main topic Immunotherapy toxicities as chapter 2 and finally its management for chapter 3

CHAPTER I

Immunotherapy

1. Immunotherapy

1.1. Definition

Many cancers have been treated by immunotherapy which is considered one of the armamentariums for cancer care **(Hernando-Calvo *et al.*, 2022)**. It is a groundbreaking treatment that dynamically modulates the immune system to attack cancer cells in a variety of targets and directions. This promising therapy is primarily exploited to strengthen the immune system by regulating the immune microenvironment, in such a way that immune cells can attack and erase tumor cells with numerous significant nodes **(Tan *et al.*, 2020)**. Furthermore, it has been a game changer in cancer care in view of the fact that it does not directly targeting cancer cells, but the patient himself, in order to re-establish effective antitumor immunity **(Dubois *et al.*, 2019)**.

Oncological immunotherapy may be described as manipulating the immune system for the recognition and the destruction of cancer cells **(Addeo *et al.*, 2021)**. This therapy is not the only kind of treatment but rather a broad range of management approach that leverage the immune system's capacity to fight disease (figure 01) **(Porcu *et al.*, 2019)**. Immunotherapy can cause the immune system to consider cancer as a bacterium or virus, and thus attack cancerous cells **(Crichton, 2017)** by directing effector T cells to tumor cells that express a particular antigen, cancer immunotherapy may enable more precise killing **(Ruan *et al.*, 2022)**.

The treatments currently used aim to release or restore the action developed by the patient’s immune system against his tumour, in order to reduce it, or even eliminate it because the "memory" immune system is capable of recognizing and eliminating a possible resurgence of cancer cells **(Pérol, 2018)**. Immunotherapy seeks to balance the immune system in order to eradicate cancer cells without inducing unchecked autoimmune inflammatory reactions that would otherwise restrict its therapeutic potential **(Abbott and Ustoyev, 2019)**.

The novelty comes from the use of drugs which no longer target the cancerous cell but stimulate the body's defences against tumour cells, exerted by the immune system. The immune system's ability to turn on (or off) molecules known as "checkpoints" to trigger an immune response is a crucial component. However, more recent medications have been able to target these checkpoints to aid in the fight against cancer. Cancer cells frequently employ these checkpoints to evade immune system attacks **(Johnson *et al.*, 2019)**.

The goal is to break the tolerance of this system to cancer cells and allow the patient's immunity to react against his disease with long-lasting reaction by using various strategies which been authorized by the Food and Drug Administration (FDA) :

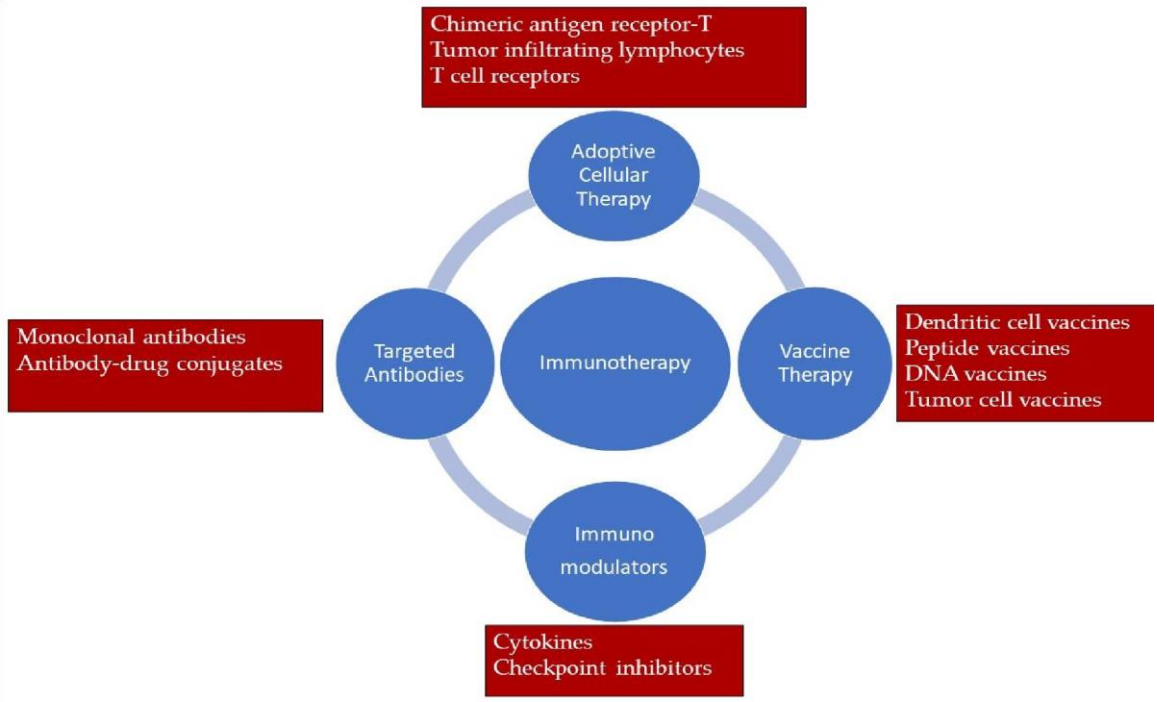

Figure 01. Immunotherapy approaches for cancer treatment **(Akkin *et al*, 2021)**

1.2. History

Cancer immunotherapy, a treatment that directly enhances a patient's immune system, is typically perceived as a modern innovation. However, scientific efforts to modulate the immune response to combat cancer occurred as early as the nineteenth century. In fact, the discovery, development, and enhancement of immuno-oncology represent a rich history.

Initial evidence of immunomodulation affecting cancer meant that bacterial toxins were used. Two German physicians, W. Busch and Friedrich Fehleisen, found spontaneous tumor regressions in patients inadvertently infected by erysipelas, a bacterial skin infection. Following these anecdotal findings, Busch saw tumor narrowing after intentionally infecting a patient with erysipelas cancer in 1868. In 1882, Fehleisen defined the specific bacterial toxin, *Streptococcus pyogenes* that caused erysipelas leading to tumour regression in patients with multiple types of cancer.

As a result of these findings, attempts have been made in the U.S. to modify the immune system to treat cancer. William Coley injected a bacterium into the sarcoma, Signor Zola. Amazingly, Zola survived another 8 months with this treatment. Coley's research included over 1,000 tumor regressions and cures in patients with a variety of malignant tumors, notably lymphoma, sarcoma and testicular cancer. Coley's "toxins" came onto the market in 1899; but many oncologists feared infecting their patients with bacteria, making immune-based toxin therapies almost forgotten by the medical community for decades.

During the mid-1990s, critical immune mediators called T-cells were discovered. An Australian team first reported the functionality of T cells in mice in 1967. Only in 1982 did James Allison and his colleagues Bradley McIntyre and David Bloch characterize T-cell receptors. 9 later, a Belgian team released the first report on the recognition of T cells in human melanoma antigens. By 1996, Allison's team detected that the blocker protein called CTLA-4, which regulates the immune response to prevent auto-immunity, was causing tumor releases in mice. The researchers correlated a further subset of T cells that impart sustained immune memory with clinical response in colorectal cancer patients a decade later.

Immunoblockers (IBI) appeared to be a brilliant approach for the treatment of many cancers. IBIs target precise tracers on immune or tumor cells, enabling the immune system to attack cancer cells. In 2011, the original IBI, a CTLA-4 blocker named Ipilimumab, was approved by the FDA. By 2016, the FDA approved another two CIs, anti-PD-1 (pembrolizumab) and anti-PD-L1 (atezolizumab).

Chimeric antigen receptor T (CAR T) cells have great potential in the treatment of many cancers, including leukemia. After the extraction of a patient's T-cells, CAR T cells are designed to recognize and target markers found on cancer cells. Such therapies have revolutionized the treatment landscape **(Kokolus, 2021)**.

The 1970s, monoclonal antibodies were set up in the laboratory and endorsed by the FDA for clinical use in 1997. These antibodies act by binding to specific proteins on the surface of cancer cells, signaling their destruction by the immune system. Since that time, many more monoclonal antibodies have been designed and approved for use in various cancers **(Abbott and Ustoyev, 2019)**.

Oncolytic vaccines were first used in the 1920s, but after deaths from the Calmette-Guerin (BCG) vaccine in the 1930s, this treatment was put on hold until 1976. The FDA has approved the first cancer vaccine, sipuleucel-T, for castrate-resistant prostate cancer in order to expand overall patient survival. Their limits have been a lack of understanding of how to inoculate patients. To obtain a cytotoxic response to T cells as well as to circumvent and/or inhibit the tumor microenvironment to obtain an anti-tumor response. Up to 1990, clinically efficacious oncolytic vaccines were still intangible **(Dobosz *et al*., 2019)**.

Immunotherapy has become more significant in recent years as a means of treating leukemia, lymphoma, and multiple myeloma. Additionally, they are incorporated into typical regimens and have been used in recent treatments for hematological malignancies. This is true for monoclonal antibodies and immunomodulatory medicines, for which novel compounds or combination therapies are being developed. Additionally, a lot of clinical trials are being published in the present research on treatments for hematological malignancies that are based on immunotherapy. Undoubtedly, a combination of immunotherapy and chemotherapy methods will be necessary in the future to treat hematological tumors that currently resist remission **(Lanier *et al*., 2022)**.

1.3 Immunoediting

Although Coley never fully understood the mechanism of action of his toxin (a cocktail of heat-killed bacteria), he amassed a wealth of evidence linking the immune system to cancer. Years later, the immunosurveillance hypothesis would provide more details and develop this connection. Paul Ehrlich first proposed in 1909 that the immune system has the ability to recognize, manage, and eradicate cancer cells **(Carlson *et al*., 2020)**. The notion of cancer immunosurveillance was initially put forth in 1957 by Thomas and Burnet, who explained that lymphocytes serve as guardians, recognizing and removing cells that have acquired mutations and differ from healthy host cells **(Abbott and Ustoyev, 2019)**. Initially rejected, the idea is now recognized as a part of cancer immunoediting, in which the surveillance system can choose or "shape" the immunogenicity of tumor cells that are not initially eradicated **(Oiseth and Aziz, 2017)**.

Following a series of experiments using brand-new, especially immunocompromised mouse strains, the concept of immunosurveillance was finally demonstrated in the early 2000s. Since the immunosurveillance theory was first forth, the interaction between the immune system and cancer has been honed and given the new moniker "immunoediting"

(Carlson *et al.*, 2020). It is a dynamic period during which immune cells initially eradicate tumor cells and ultimately a period during which cancer cells are able to avoid immune system destruction through a variety of processes. Since it includes all stages of cancer and immune system interaction beyond immunosurveillance, the term "immunoediting" has gained popularity **(Abbott and Ustoyev, 2019)**.

According to the theory of immunoediting, the immune system and cancer collide at three different stages: elimination, equilibrium, and escape (figure 02).

1.3.1. Elimination phase

Elimination, the first stage of immunoediting, defines the period of ongoing active immunosurveillance, which is typically regarded as the time of undetectable and initial tumor formation. By immunosurveillance, the immune system can detect and kill cells that are malignant or potentially malignant but are not routinely fixed by the innate hereditary DNA repair mechanisms **(Abbott and Ustoyev, 2019)**. The elimination phase describes the immune response in which the innate immune system recognizes and eliminates developing tumor cells, followed by the presentation of tumor antigens in cell debris to dendritic cells, which then present them to T cells and generate tumor-specific CD4+ and CD8+ T cells **(Oiseth and Aziz, 2017)**. When only a portion of the tumor cells are removed, the elimination can either be total, meaning no tumor cells remain, or incomplete **(Sarasola *et al.*, 2021)**.

1.3.2. Equilibrium phase

During equilibrium, tumor cells that were not eliminated by the immune system during the elimination phase exert opposing pressures, leading to tumor containment. When cancer progresses and undergoes further mutations, the immune system gradually eliminates immunogenic cells while leaving behind non-immunogenic cells **(Carlson *et al.*, 2020)**. Other types of tumor alteration, such as loss of antigen presentation, decreased PD-L1 expression due to epigenetic modifications, or decreased IFNγ secretion by T cells, may also be a part of this selection process instead of tumor clone death. These immunoedited cancers can then transition into the escape phase and manifest as clinically identifiable malignancies **(O'Donnell *et al.*, 2019)**.

1.3.3. Escape phase

The remaining cancer cells that manage to escape at this final stage of evasion or escape may do so by expressing fewer antigens on their surfaces or even by abandoning their MHC class I expression. They may also demonstrate the capacity to defend against T-cell assault by expressing immune checkpoint molecules on their surfaces in the same manner as

regular cells; these IC molecules are upregulated by cytokines produced by activated T-cells and are a typical example of a negative feedback loop that controls excessive tissue damage from inflammation by downregulating or suppressing T-cells **(Oiseth and Aziz, 2017)**. As a result of the immune system's overwork and inability to control the growth of malignant cells, cancer has entirely evaded detection and can no longer be interrupted. Instead, it spreads fast, unrestrained, and violently **(Abbott and Ustoyev, 2019)**.

Thus, the prime purpose of cancer immunotherapy is to overcome the years to decades of immunoediting to produce antitumor immunity adequate to totally eradicate the patient's cancer and heal their sickness. **(Carlson *et al*., 2020)**

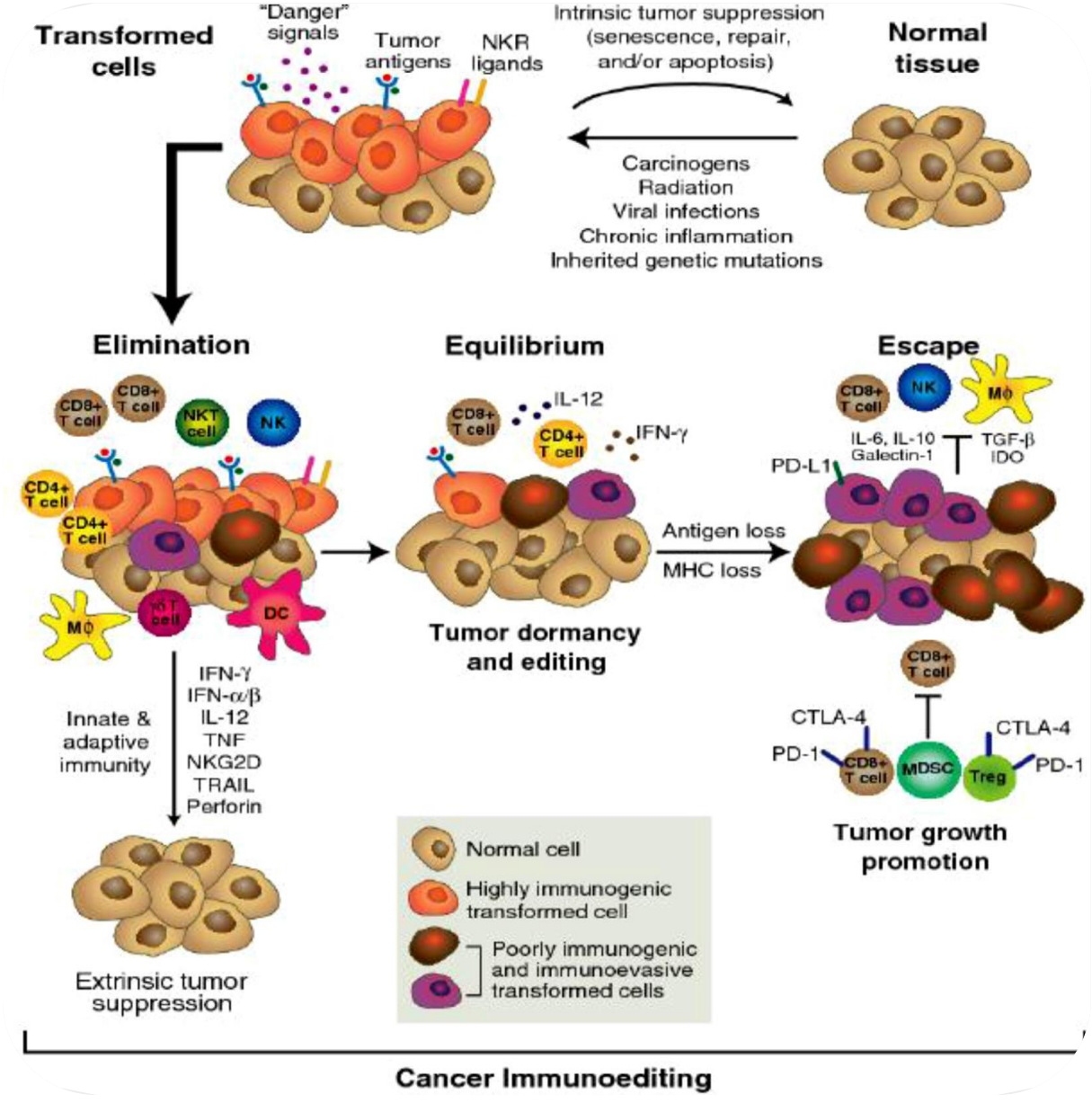

Figure 02. Cancer surveillance and immunoediting **(Abbott and Ustoyev, 2019)**

1.4. Immunotherapy approaches

The two basic components of cancer immunotherapy are typically active and passive. The foundation for this classification is the therapeutic's mode of action and the patient's immune system health.

In passive immunotherapy, the body's low-level expression of molecules or *ex vivo* activation of cells corrects improper immune responses. For people whose immune systems are ineffective against cancer, they are often taken into account. In contrast to active immunotherapy, passive immunotherapy has only had short-term effects, and it may require more administrations before it is effective.

The goal of active immunotherapy is to stimulate immune system effectors *in vivo*. For active immunotherapy to be effective, the immune system's condition must be favorable. In this instance, the immune system responds to the stimulus, is appropriately activated, and carries out the effector tasks.

The primary objective of active immunotherapy is to activate a robust and long-lasting immune response **(Keshavarz-Fathi and Rezaei, 2019)**.

1.4.1. Passive immunotherapy for cancer

1.4.1.1. Adoptive cell therapy

Adoptive cell therapy involves removing immune-competent cells from cancer patients, genetically altering or massively enlarging those immune-competent cells in a lab setting to increase immune activity, and then reinjecting those immune-competent cells back into the cancer patient to increase the body's anti-tumor immune function. Lymphokine-activated killer (LAK), chimeric antigen receptor (CAR)-modified T (TCR-T), chimeric antigen receptor-modified natural killer (CAR-NK), cytokine activation killing (CIK), and tumor-infiltrating lymphocytes (TILs) are examples of immune-competent cells. TILs, TCR-T cells, and CAR-T cells are the most researched of all ACT treatments **(Yang *et al.*, 2022)**.

In order to create CAR T cells, patient T cells must first be collected and then genetically altered to develop chimeric antigen receptors on the cell surfaces. Cells multiply over the course of two to three weeks until an enough quantity is ready for systemic injection into the patient's circulation. Some people advocate for an observation period of at least nine days. The cells are administered and observed for a duration spanning from days to weeks during hospital admission (figure 03) **(Chhabra and Kennedy, 2022)**.

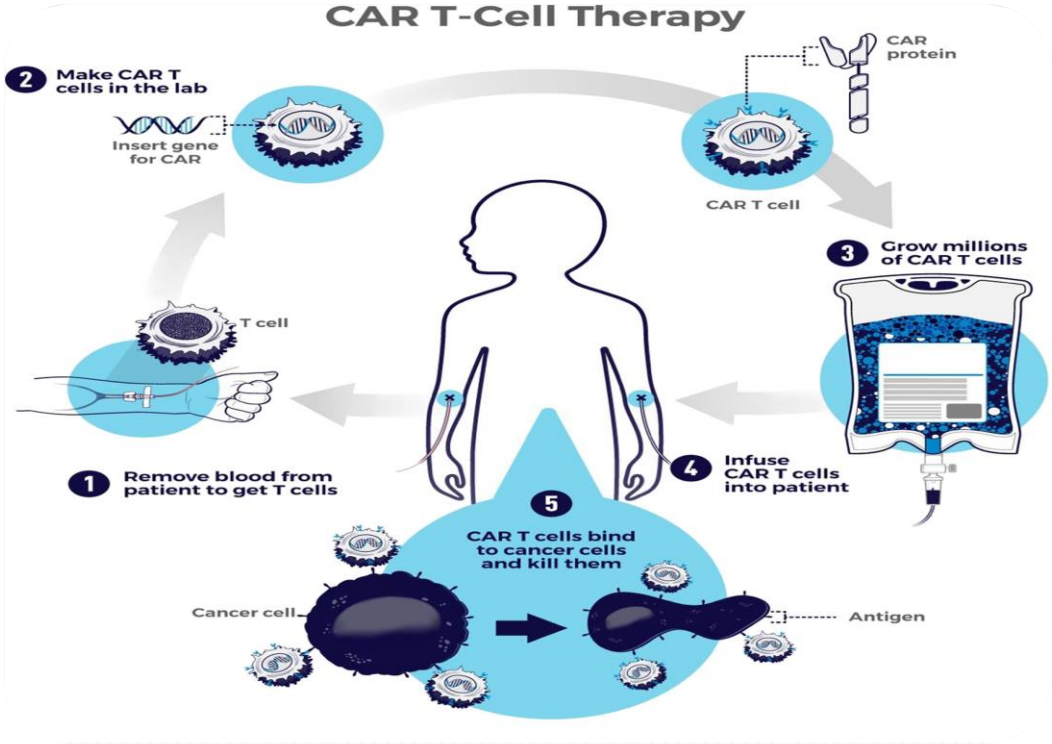

Figure 03. CAR T cell therapy procedure **(Chhabra and Kennedy, 2022)**

1.4.1.2. Cytokines

Cytokines are polypeptides, proteins, or glycoproteins that play a role in communicating the signals of cell division, growth, inflammation, and anti-inflammatory activity. Cytokine therapy's key characteristic is its ability to directly urge immune cells' development and activation **(Yang *et al.*, 2022)**. The most often used cytokine class in immunotherapy, interleukins and other interferon, has demonstrated a critical role in immunotherapy **(Kumar *et al.*, 2021)**. Among these, IFN-a possesses anticancer activity that may be classified into impacts on immune cells and tumors, it involves apoptosis and slows down cell proliferation in malignant cells. As a potential immunotherapy for both cancer and autoimmune disorders, IL-2 has the capacity to increase both regulatory T cells (Tregs) and effectors. Antigen-presenting cells (APCs) that are stimulated by an antigen secrete IL-12, which polarizes CD4+ T cells into Th1 cells and boosts CD8+ T cells, NK, and NKT cells. **(Keshavarz-Fathi and Rezaei, 2019)**.

1.4.1.3. Monoclonal antibodies

Antibody-based immunotherapy is a distinct treatment method; its unique effector actions are linked to the antibody's Fc region, which is coupled to the host immune system components, and the Fv region's simultaneous affinity to engage with its targets. The three main ways that antibodies work are antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cell

phagocytosis (ADCP), and complement-dependent cytotoxicity (CDC) **(Taefehshokr *et al.*, 2019)**.

A succinct definition of monoclonal antibodies (mAbs) is an antibody that binds to a particular region of an antigen. Because of the remarkable specificity of monoclonal antibodies in attaching to cancer cells, their adoption in cancer treatment seemed unavoidable. The interest in mAbs has grown, particularly after the identification of tumor-specific antigens. Both alone and in conjunction with other anticancer medications, MAbs can be utilized to treat cancer. This scientific method, known as antibody-drug conjugate, tries to deliver anticancer medications to the tumor through mAbs made particularly for the cancer cell surface antigen (figure 04) **(Akkin *et al.*, 2021)**.

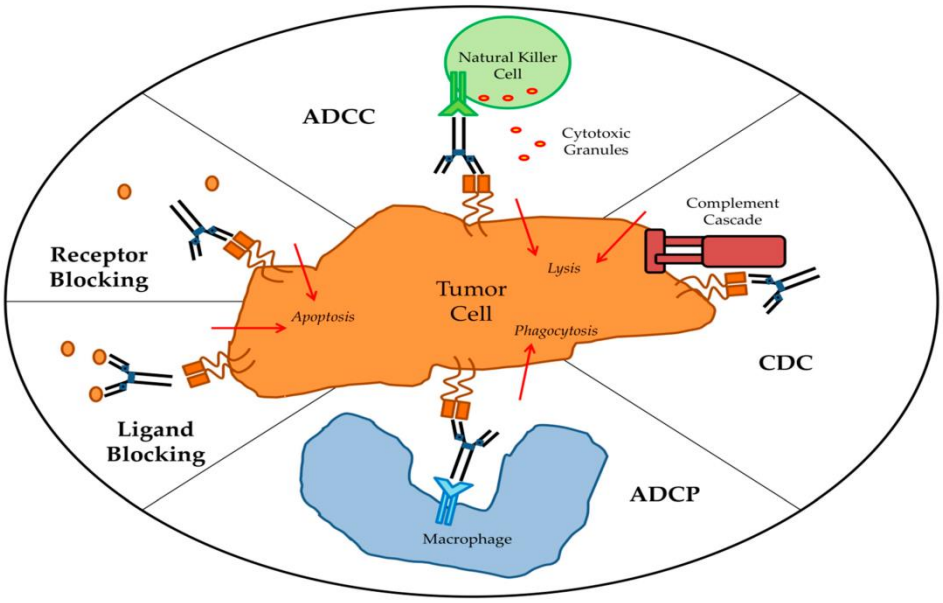

Figure 04. Antibody effector mechanism **(Zahavi and Weiner, 2020)**

1.4.2. Active immunotherapy for cancer

1.4.2.1. Cancer vaccines

A form of active immunotherapy where the primary goals are to activate the immune system, eliminate the tumor, and prevent relapse is the use of vaccines in cancer immunotherapy. In order to increase the number and activity of tumor antigen-specific CTLs and develop memory immunological responses against tumors, cancer vaccines are responsible for presenting particular antigens expressed on the surface of cancer cells to the immune system. The understanding of the architecture of tumor-associated antigens unique to cancer cells has increased interest in cancer vaccinations. They are developed into both preventative and

therapeutic vaccines, such as vaccines against the human papillomavirus (HPV), which has been linked to several cancers, including those of the throat, vagina, and cervical regions, and Sipuleucel-T (Provenge), the first commercially available cancer vaccine, which is a dendritic cell-based vaccination designed for the treatment of hormone-refractory prostate cancer (figure 05) **(Akkin *et al.*, 2021)**.

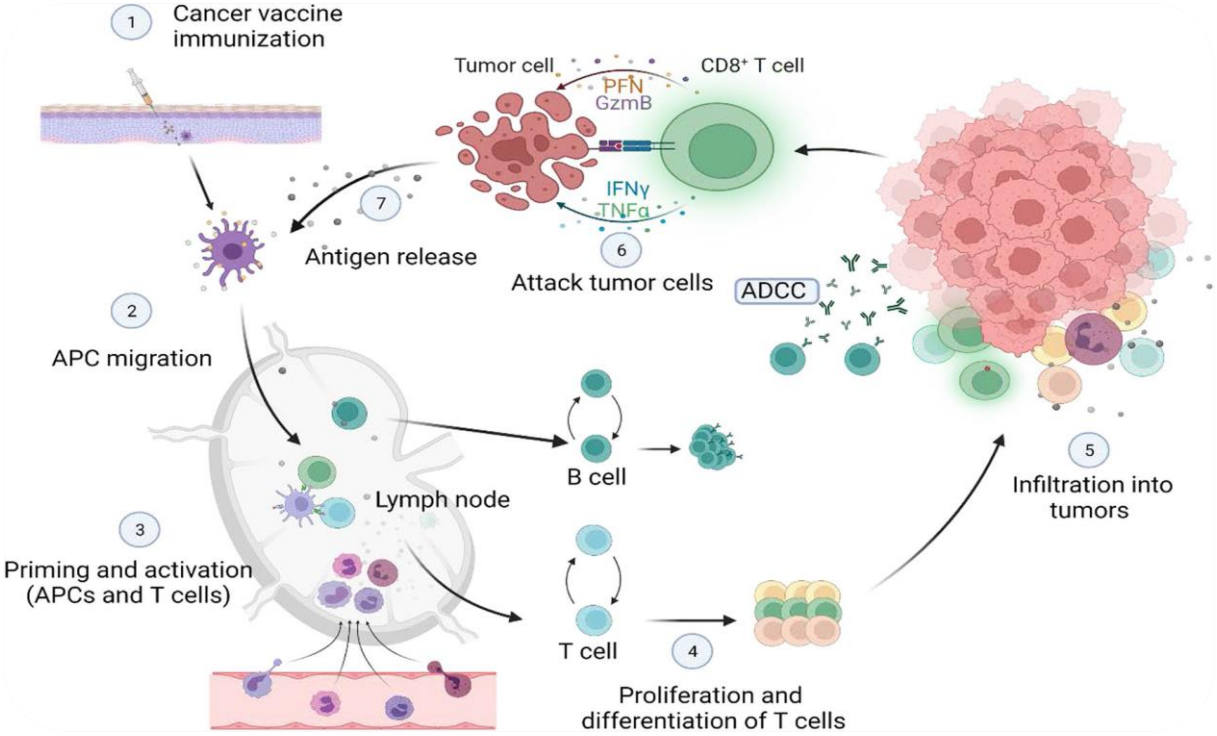

Figure 05. Tumor-immune cycle induced by cancer vaccines **(Liu *et al.*, 2022)**

1.4.2.2. Immune checkpoint inhibitors

Monoclonal IgG antibodies known as ICIs work by stifling inhibitory signals that deactivate cellular immune effector cells. Immune checkpoints have a physiological function in which they "switch off" cytotoxic T-cells to suppress the immune response and so promote self-tolerance. To prevent tissue damage from T-cell activation, native cells use these checkpoints.

By connecting with the receptors on cytotoxic T-cells, some cancer cells take advantage of these checkpoints to avoid host defenses. Hence, immune checkpoints are a potential therapeutic target as well as a way through which cancer cells might evade immune surveillance. ICIs enable T-cells to stay active and attack cancer cells by obstructing the communication between immunological checkpoints and these cells. Cytotoxic T-lymphocyte antigen 4 (CTLA-4), programmed death receptor 1 (PD-1), and its ligand, programmed death-ligand 1 (PD-L1), are the current surface receptor and ligand targets for ICIs. Due to the overexpression of certain

receptors and ligands in specific tumor microenvironments, they are effective in the treatment of cancer (figure 06) **(Chhabra and Kennedy, 2021)**.

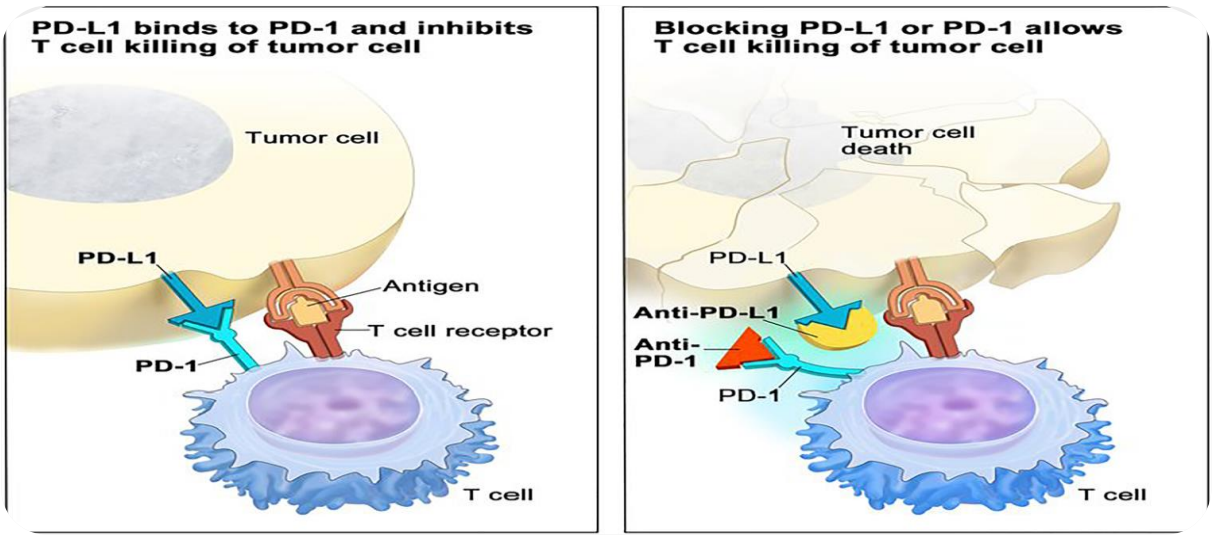

Figure 06. Immune checkpoint blockade mechanism of action **(Chhabra and Kennedy, 2021)**

1.4.2.3. Oncolytic viruses

Cancer is treated with oncolytic viruses using a combination of two interrelated mechanisms: immune activation and targeted tumor cell destruction. Several methods are used in the engineering of OVs to selectively lyse tumor cells. Viral entry receptors are abundantly expressed in tumor cells in comparison to non-tumor cells, and these receptors allow OVs to enter cells. Tumor cells, which frequently exhibit higher levels of replicative activity than non-tumor cells, experience increased viral replication. The lack of type I interferon antiviral signaling in tumor cells also facilitates selective OV replication within tumor cells. Both innate and adaptive immunity are induced by viral replication in the tumor microenvironment. Viral and tumor antigens, including damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs), are shown as a result of cellular lysis. These antigens stimulate the host's cytotoxic and helper T lymphocytes. The immunosuppression that is frequently present in the tumor microenvironment may be overcome by this immune activation, enabling immune-mediated tumor cell targeting. There is some data that suggests using immune checkpoint inhibitors in conjunction with treatment may help this immune activation even more (figure 07) **(Chhabra and Kennedy, 2022)**.

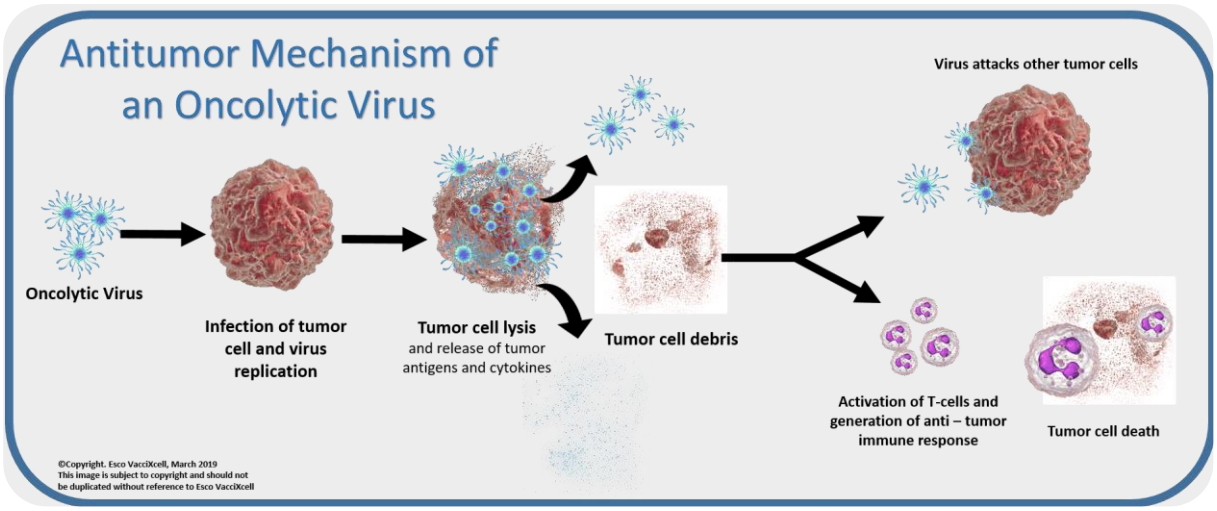

Figure 07. Mechanism of an oncolytic virus **(Esco Healthcare, 2019)**

CHAPTER II

Immunotherapy toxicities

2. Immunotherapy toxicities

2.1. Adoptive cellular therapy

2.1.1. Cytokine Release Syndrome

Both tumor lysis syndrome (TLS) and cytokine release syndrome (CRS) are types of systemic toxicity associated with CAR T cell treatment. The overlap of these two entities makes diagnosis more difficult. Target cell apoptosis, which is the hallmark of TLS, may be accompanied by electrolyte abnormalities such hyperuricemia, hyperphosphatemia, and hyperkalemia. Despite the fact that CRS can happen with other immunotherapy treatments and disease processes, it is more frequent with CAR T cell therapy. The presence of hyperthermia without a known viral cause characterizes cytokine release syndrome, an acute systemic inflammatory condition. Increased levels of the cytokine interleukin 6 (IL-6) and capillary leakage are common symptoms of CRS. It is brought on by an unbalanced immune reaction to the CAR T cell-mediated killing of hyperproliferative target B cells (or other oncologic targets). After the start of CAR T cell therapy, symptoms can appear anywhere from minutes to weeks later, with the majority of patients displaying symptoms within two weeks. The chance of developing either TLS or CRS is predicted to increase with the burden of cancer, and the amount of CAR T cells given may have an impact on whether CRS develops **(Ayers *et al.*, 2022)**.

2.1.2. Cardiovascular

The CAR T cell therapy has the potential to be harmful to the heart and blood arteries. Vascular toxicity frequently occurs when CRS is present. There have been no examples of medium- or large-vessel vasculitis that can be clearly linked to CAR T cell therapy, but CRS can cause venous capillary leakage and hypotension. Heart failure is the most frequent cardiovascular hazard, occurring in 15% of patients within 30 days of medication. Following therapy, toxicity can happen minutes, hours, or even days later and is related to both the severity of the disease and the quantity of T cells infused. The theory of "off target, off organ" toxicity, or the possibility that CAR T cells made to target a particular antigen on a target cell may also harm an organ in another part of the body through a common antigenic epitope, is the best way to understand direct cardiac toxicity. When CAR T cells were directed against the testis antigen MAGE-A3, toxicity that was not directly related to CRS was seen. T lymphocytes created to fight MAGE-A3 may recognize a common peptide structure with the myocardial protein titin, and deadly cardiovascular damage may result. Numerous patients, including one who developed neutropenic fever three days after receiving CAR T cell therapy and progressed to shock and hypoxia, have experienced fatal direct cardiac toxicity attributable to this shared peptide

structure. The patient's serum troponin-I level was found to be increased to 54.4 ng/mL, and an ECG revealed extensive ST-segment abnormalities. Cardiogenic shock ultimately caused the patient's death, and an autopsy revealed that the myocardium had been extensively invaded by T cells. The left anterior descending artery had a thrombus, but there was also significant myocardial necrosis that couldn't be explained by the location of the artery. Toxicologists should be aware of this particular pattern of toxicity even if percutaneous coronary angiography is still the gold standard of therapy for ST-elevation myocardial infarction. Similar symptoms developed in a second patient receiving CAR T cell therapy for myeloma that was resistant to conventional therapy, and that patient later passed away from cardiogenic shock that was worsened by cardiac tamponade. Despite not having a blocked coronary artery, this patient demonstrated signs of Tcell invasion and myocardial necrosis (figure 08) **(Montisci *et al*., 2021)**.

2.1.3. Gastrointestinal and Hepatic

Similar to the mechanisms causing cardiovascular toxicity, CRS or a number of different on- and off-target pathways could be to blame for gastrointestinal system toxicity. Following CAR T cell induction, severe inflammatory colitis has been linked to CAR T cell therapy that targets carcinoembryonic antigen (CEA). Emesis, diarrhea, and colitis, which can appear within days, are common gastrointestinal side effects independent of CRS that can affect 15% of individuals receiving CAR T therapy. Direct gastrointestinal poisoning symptoms and CRS symptoms are comparable **(Dahiya *et al*., 2020)**.

Hepatotoxicity is another frequent side effect, affecting 7–11% of patients and manifested by an increase in the serum levels of aspartate and alanine aminotransferases as well as bilirubin. Following the infusion of CAR T cells, it may happen right away or months later. It might be brought on by common peptide epitopes in hepatocytes and canalicular cells that have on-target effects. Due to the variable expression of surface epithelial carbonic anhydrase IX, biliary toxicity has been noted following CAR T cell therapy for renal cell cancer. A biopsy's histologic results showed purulent cholangitis and bile duct infiltration, and flow cytometry verified the presence of modified T cells in the injured tissue.

2.1.4. Neurologic

The neurologic damage connected to CAR T cell therapy is known as immune effector cell-associated neurotoxicity syndrome (ICANS). It can happen to up to 40% of patients, making it widespread. It can manifest with symptoms ranging from tremor to necrotizing encephalopathy, coma, and death, and is frequently treatable with supportive care. Other

manifestations can take the form of delirium, aphasia, focal or generalized seizures, cerebral edema, agitation, and word finding issues. While signs and symptoms of ICANS typically appear 4-5 days after infusion, they can appear right away or take much longer. Although most neurologic toxicity manifests as global symptoms, focal deficits such as mydriasis or motor weakness can also develop. Cerebral edema from CRS is frequently blamed for CAR T cell neurotoxicity, however the pathogenesis of this condition is not well understood. A root-cause analysis revealed that enormous cytokine release and alterations in vascular permeability contributed to the fatalities related with cerebral edema that caused the ROCKET trial of JCAR015 CAR T cells to be stopped. This is significant because the study was ended due to fatalities associated with cerebral edema **(Ayers *et al*., 2022)**.

2.1.5. Pulmonary

Although CAR T cell therapy has only rarely been linked to direct pulmonary toxicity, hypoxia and respiratory distress are frequently seen in the context of CRS. In one case, after receiving a massive dosage of modified T cells (1010 cells), a patient with metastatic colon cancer experienced hypoxia and respiratory distress 15 minutes later. Massive CRS was discovered, and the patient eventually passed away. According to autopsy findings, the pulmonary damage was caused by minute levels of ERBB2 protein on pulmonary epithelial cells that were detected by modified T cells **(Brudno and Kochenderfer, 2016)**.

2.1.6. Renal

Although acute kidney injury (AKI) is a potential side effect of CAR T cell therapy, it is less frequently linked to direct organ-specific toxicity and more frequently occurs in conjunction with TLS, CRS, or renal hypoperfusion caused by hypotension. In early CAR T cell treatment trials, electrolyte problems, such as hypophosphatemia and hypokalemia, were the most often observed disturbances. Adult patients receiving CAR T cell treatment for diffuse large B-cell lymphoma developed acute kidney injury in 19% of cases, acute tubular necrosis in 8% of cases, and renal replacement therapy (RRT) was needed in 6% of cases. It was believed that these results were secondary to either CRS or blockage without direct nephrotoxicity. With a death rate of 67% after 60 days, acute tubular necrosis seems to indicate a dismal prognosis. In this study, it was noted that nephrotoxicity happened roughly 6–10 days after CAR T cell treatment was administered. All patients who had RRT eventually passed away within 30 days **(Brudno and Kochenderfer, 2016)**.

2.1.7. Miscellaneous

Except in situations where modified T cells targeted to epithelial tissue detect protein epitopes on sensory organs like the eyes, ears, and skin, such as during the treatment of melanoma, severe CAR T cell toxicity is primarily restricted to the organ systems above. In one prospective series, ocular or auditory damage, including anterior uveitis and hearing loss, occurred in 14 of 36 patients receiving melanoma treatment with MART-1- or gp100-specific T cells **(Chhabra and Kennedy, 2022)**.

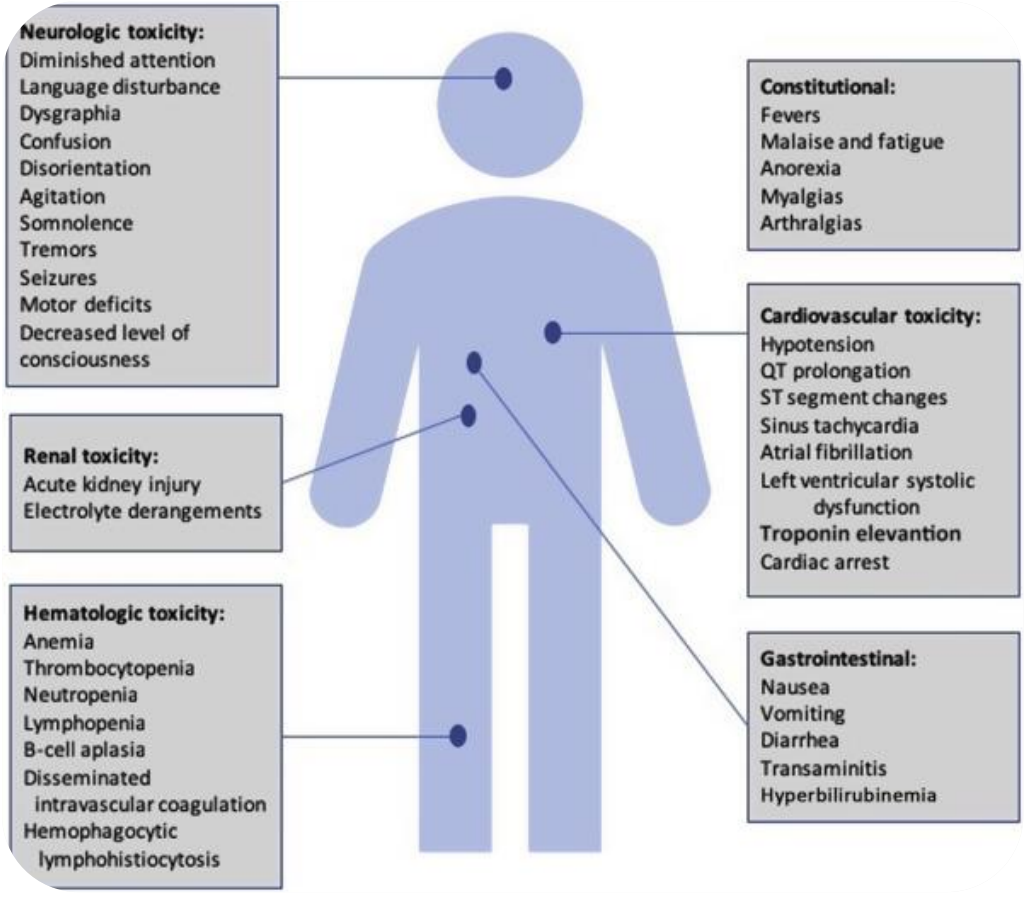

Figure 08. Significant multiorgan toxicities can be associated with chimeric receptor antibody (CAR) T-cell therapy **(Ghosh *et al.*, 2020)**.

2.2. Cancer vaccines

Despite the fact that there have been cancer vaccines accessible since the 1970s, only one, called Sipuleucel-T, has been approved for use in cancer therapy with the goal of improving patient survival in two trials for patients with metastatic castration-resistant prostate cancer. In general, cancer vaccinations are well tolerated, with the most common grade 1 toxicities being chills, fever, exhaustion, back discomfort, nausea, erythema, and itching at the injection site. However, over grade 3 AEs are also infrequently noticed. Instead of vaccine dosages, types of vaccines are linked to toxicities in cancer patients. Virtually no cancer vaccines typically result in toxicities other than very minor ones. Perhaps this is because a large number of tumor-associated antigens are frequently overexpressed or undetectable in normal cells, but significantly overexpressed in cancer cells. For instance, the majority of melanoma vaccines work by directly interacting with the differentiation antigen of melanoma cells; as a result, modest immune toxicities, like vitiligo, might infrequently occur but are often indicative of a positive therapeutic response. Of course, a modest sample size is used in preclinical or phase I–II clinical studies where the great majority of cancer vaccines are evaluated (figure 09) **(Yang *et al.*, 2017)**.

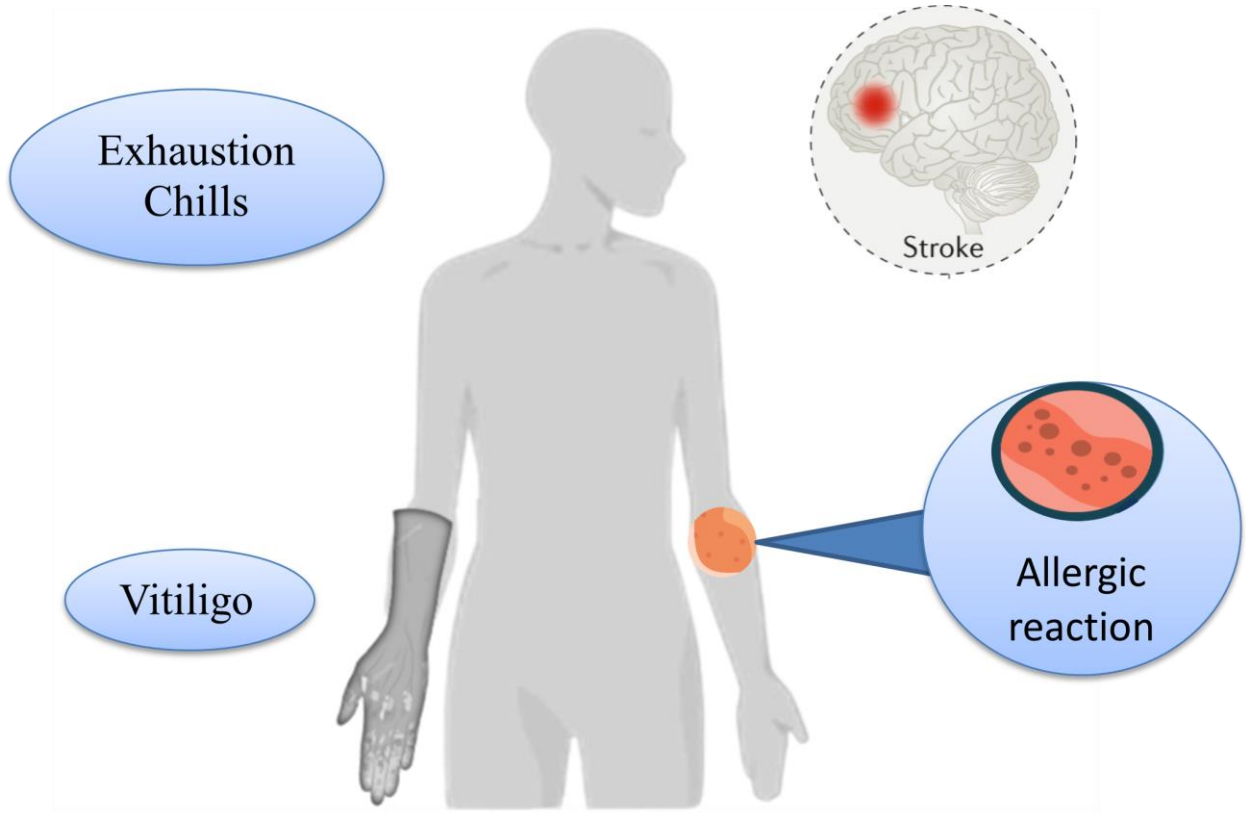

Figure 09. Cancer vaccines toxicity

2.3. Cytokines

2.3.1. IFN-a

In studies on hairy cell leukemia, melanoma, renal cell carcinoma (RCC), and other solid tumors conducted in the 1980s, IFN-a was found to be crucial in the development of anticancer activity. Even though IFN is a natural substance, contrary to initial hopes, it has not shown to be a harmless therapeutic. Although they affected several organ systems, headache and myalgia, which are characterized as flu-like symptoms, were the most frequent systemic toxicities of IFN therapy. Fatigue and fever (which varied from 60% to 70%) were the next most common side effects. In accordance with information from 143 patients who received high-dose IFN-a treatment in the Eastern Cooperative Oncology Group (ECOG) Trial E1684, 66 individuals reported experiencing nausea and vomiting after receiving IFN, and 2/3 of the patients also reported early satiety, anorexia, and weight loss. The main side effect of dose limitation is myelosuppression because large doses of interferon-a-2b prevent megakaryocytic progenitor cells from proliferating and activating in a non-lineage-specific way. Although 65% of patients (92/143) in the E1684 study receiving high-dose IFN-a reported developing neutropenia, IFN rarely leads to neutropenic fever or sepsis and is rarely a reason to stop treatment. Anemia and thrombocytopenia were seen in roughly 10% of patients receiving IFN therapy. Although thrombocytopenic purpura and progressive anemia are uncommon, IFN must be permanently stopped. Two deaths from hepatotoxicity were reported in a pilot investigation of IFN adjuvant therapy for high-risk melanoma patients. Although mild elevations in hepatic enzymes without clinical symptoms are typical, liver function should be assessed at baseline, particularly in the presence of hepatitis B or C, weekly during induction, monthly during the first three months of maintenance, and then every three months during the remaining therapy. It is generally agreed upon that IFN administration should be stopped in patients with grade 3 liver toxicity until the transaminase levels returned to within 1.5 times of normal, and that IFN dosage should be at least 30% lower if it is to be resumed. Some IFN adverse effects, such as autoimmune disorders, a biomarker linked to a favorable prognosis, are fully unaffected by dose and duration. Patients receiving IFN frequently have thyroid dysfunction (hyperthyroidism or hypothyroidism), with a prevalence of 10% to 15%. All patients should have their T3 and T4 levels, as well as their thyroid autoantibodies, checked because hypothyroidism typically develops after a protracted period of hyperthyroidism. The uncommon Sarcoidosis has skin lesions that resemble subcutaneous metastases or mediastinal lymph nodes and exhibits strong Fluorine-18 deoxyglucose (FDG) absorption in positron emission tomography, suggesting that it most likely has an immunological etiology. There are also reports of vitiligo, lupus, rheumatoid arthritis,

polymyalgia rheumatic, and psoriasis. IFN should be administered cautiously to patients who already have an autoimmune disease since the subsequent IFN therapy typically results in more severe side effects that may affect the immune system's memory function. In as many as 24% of patients, depression and irritability are the most frequent neuropsychiatric side effects. However, IFN-a has also been linked to acute confusional states, anhedonia, fatigue, apathy, sleep disturbances, sexual dysfunction, impaired memory, cognitive dysfunction, and suicidal ideation. Typically, neuropsychiatric effects are mild to severe and go away within two to three weeks of stopping IFN. Neuropsychiatric toxicities, however, can linger in some patients for weeks, months, or even years **(Yang *et al*., 2017)**.

2.3.2. IL-2

Based on its sustained anticancer effects in patients with advanced RCC or melanoma, the FDA approved high-dose cytokine of IL-2 in 1998. High doses of IL-2 should only be delivered under the guidance of trained medical professionals who are knowledgeable in anticancer medications. To treat severe IL-2 toxicities including pulmonary edema and hypotension, an intensive care unit and doctors trained in cardiopulmonary monitoring or hemodynamic support are required. Single-agent IL-2 recipients with metastatic RCC experienced a drug-related mortality incidence of 4% (11/255) and 2% (6/270) respectively. Chills, fever, and exhaustion, as well as nausea, vomiting, diarrhea, hypotension, increased transaminases, dyspnea, hyperbilirubinemia, and oliguria, are typical IL-2 toxicities. Capillary leak syndrome (CLS), which is characterized by a loss of vascular tone and extravasation of plasma proteins and fluid into the extravascular space, starts right away following treatment with IL-2 at the indicated dosages. Hypotension can ensue from CLS, and the decreased organ perfusion may be too severe to prevent death. In addition to prerenal azotemia, pulmonary edema, angina, myocardial infarction, pleural effusion, and supraventricular and ventricular cardiac arrhythmias, CLS may also be accompanied by alterations in mental status. As a result, only patients with healthy cardiac and pulmonary systems should receive IL-2. Patients with a history of cardiac or pulmonary disease who underwent a normal thallium stress test and a normal pulmonary function test should be treated with extreme caution. High-dose IL-2 therapy results in thrombocytopenia, anemia, and impaired coagulation function. Clinical experiments have nonetheless demonstrated that after IL-2 withdrawal, autoimmunity, neurotoxicity, and myocarditis may intensify or persist for a while (often within 4 weeks). Long-term autoimmunity reactions' origin is uncertain. In contrast to vitiligo, which may get worse or even stop responding to treatment, autoimmune illnesses like hypothyroidism take over 6 to 10 months to improve. The mild neurotoxicity of IL-2 includes irritation, lethargy, and psychosis florid, which

might manifest as a psychotic episode. Within 24 hours of the last administration, neurotoxicity peaks and needs to be promptly identified **(Yang *et al*., 2017)**.

2.3.3. IL-12

IL-12 has been shown to be effective in various preclinical tumor immunotherapy studies for nearly a decade now. According to a study comparing IL-12 with traditional chemotherapy for the treatment of lung cancer, IL-12 treatment inhibited the growth of lung tumors, which contributed to the long-term survival of mice with lung cancer. Additionally, research suggests that IL-12 may be less hazardous than other immunotherapeutics like IFNs or IL-2. Although IL-12 has positive immunostimulatory and anticancer effects, IL-12-related toxicities must be taken into account. The findings of serum liver function tests revealed that the most typical adverse effects were transitory neutropenia and thrombocytopenia, as well as fever, chills, weariness, nausea, or vomiting. It's fortunate that no patient required platelet transfusion and no one developed a neutropenic fever, proving that temporary neutropenia and thrombocytopenia were inconsequential. However, two of the three patients who received 250 ng/kg of recombinant human IL-12 experienced dose-limiting toxicities, such as diarrhea and asymptomatic elevation. As a result, patients can safely receive the recommended doses of IL-12, especially those who have undergone autologous stem cell transplantation for high-risk hematological malignancies. It is important to conduct additional tests to determine whether IL-12 is effective in the context of immunotherapy **(Yang *et al*., 2017)**.

2.4. Immune checkpoint inhibitors

Checkpoint inhibitors (CPI) have produced encouraging results in terms of tumor regression and patient survival in clinical trials for a number of cancer types. Unusual unfavorable consequences are frequent, nevertheless, as a result of non-specific immunostimulation, which can result in tissue damage, autoimmune disease, and inflammation specific to certain organs. Although higher generation of antibodies has been reported, non-cancerous tissue infiltration by dysregulated T cells is a potential source of harm.Since 2011, clinical knowledge of ICIs and the distinct side effects known as immune-related adverse effects (irAEs) has grown. There have been no well-documented reports of ICI overdose to date in the medical literature. It seems that the emergence of immunostimulation, as demonstrated by the existence of irAEs, appears to be linked to a favorable response to cancer and increased survival. Vitiligo, hypophysitis, enterocolitis, and pneumonitis are a few irAEs that have been linked to improved tumor response or lengthened survival (figure 10) **(Chhabra and Kennedy, 2021)**.

2.4.1. Cardiac

Cardiotoxicity caused by ICIs is uncommon but potentially lethal, so treating clinicians must have a high degree of suspicion. Although the true incidence may be higher, it has been estimated to occur in about 0.09% of individuals taking ICI therapy. When compared to monotherapy, combination ICI therapy carries a fivefold increased risk of ICI-related cardiotoxicity. Human cardiomyocytes express PD-1 and PD-L1, making lymphocyte-mediated cardiac damage plausible. Along with fatal cases of cardiac failure, myocarditis, dilated cardiomyopathy, pericarditis, pericardial effusion, and arrhythmias have all been documented. Severe adverse effects like myositis and myasthenia gravis have been described alongside myocarditis in certain patients with cardiac IRAEs. The usual period to beginning is 17 to 34 days after therapy begins, however it might happen 6 weeks or later. Estimates of the mortality rate from ICI-related cardiotoxicity range from 27% to 50%. Fatigue, myalgias, chest discomfort, dyspnea, and syncope are a few of the many symptoms of ICI-related cardiotoxicity **(Gumusay *et al.*, 2022)**.

2.4.2. Dermatologic

The most frequent irAEs are dermatological side effects, which affect 30–40% of patients receiving ICIs that target the PD-1 axis and 40–50% of patients receiving ipilimumab. Nivolumab poses the greatest risk among treatments targeting the PD-1 axis. Even while they rarely pose a life-threatening hazard, they may significantly lower patients' quality of life. The most typical skin irAEs include erythema, pruritus, hypopigmentation that resembles vitiligo, lichenoid responses, eczema, and morbilliform eruptions. Vitiligo appears to only be present in melanoma patients, and having it is connected with a good chance of recovering from malignancy. On occasion, papulopustular eruptions and ulcerations that resemble pyoderma gangrenosum may occur. Any of the aforementioned eruptions that cover between 10% and 30% of the whole surface area of the body (grade 2) or less than 10% of the total body surface area (grade 1) are considered low-grade dermatologic irAEs. Over 30% of the body's surface area is affected by grade 3 reactions, which also severely interfere with daily activities. Life-threatening responses are in grade 4. The exfoliative disorders Stevens-Johnson syndrome/toxic epidermal necrolysis and drug response with eosinophilia and systemic symptoms (DRESS) are examples of grade 3 and 4 reactions, which are uncommon (1-4% of dermatologic irAEs). The clinical significance of hair re-pigmentation and alopecia, which have also been described with ICI therapy, is unknown. Dermatologic side effects are dose-dependent and usually start to show up 3 to 8 weeks after the start of treatment **(Kichloo *et al.*, 2021)**.

2.4.3. Endocrine

Hypothyroidism or hyperthyroidism, thyroiditis, hypophysitis, pituitary gland dysfunction, primary adrenal insufficiency, and insulin-dependent diabetes mellitus are only a few of the common and potentially serious endocrine disorders that can occur with ICI therapy. Endocrinopathy and agent type both affect how quickly endocrine IRAEs manifest. Endocrine toxicities must be treated with hormone replacement therapy for the rest of one's life, unlike other IRAEs that can be treated and resolve **(Gumusay *et al*., 2022)**.

2.4.3.1. Thyroid

Hypothyroidism, hyperthyroidism, or thyroiditis are all signs of thyroid malfunction. Hypothyroidism can be primary (caused by a thyroid disorder) or secondary (caused by a pituitary disorder). Up to 20% of patients on ICI therapy have thyroid dysfunction, which is especially common in patients receiving anti-PD-1 therapy. This may be because PD-1 is expressed on the surfaces of all B cells, including memory B cells that secrete IgM. As a result, patients receiving treatment with ICIs based on PD-1 frequently experience antibody-mediated thyroid dysfunction. Up to 80% of patients with hypothyroidism caused by ICI exhibit anti-thyroid antibodies, underscoring the condition's similarity to autoimmune thyroid disease. Since symptoms are rare and hyperthyroidism frequently resolves on its own, it is rarely treated unless the patient exhibits severe symptoms. Within 3 to 6 weeks, hyperthyroidism brought on by ICI usually results in a lifelong hypothyroid condition. It has not been demonstrated that preventative corticosteroids can stop patients with ICI-related hyperthyroidism from developing hypothyroidism **(Varghese and Best, 2022)**.

2.4.3.2. Pituitary

Previously known as hypophysitis, pituitary gland inflammation is an uncommon condition marked by immune cells infiltrating the gland. Hypophysitis has increased in frequency since ipilimumab was approved. When using large doses of ipilimumab, the incidence of hypophysitis increases from 1-4% to up to 17%. Less than 0.5% of cases involve other ICIs. Although the precise pathophysiologic cause of this disparity is yet unknown, it may be connected to human pituitary cells' expression of CTLA-4 and the rise in antibodies made against pituitary cells. It is more prevalent in men, though this may in part be due to men having a higher prevalence of melanoma. The average interval between the start of ICI and the diagnosis of hypophysitis is 6–12 weeks, however up to 16 weeks have been documented after ICI treatment. The median time to onset is longer (11 weeks) in patients receiving low-dose

ipilimumab than with high-dose therapy, suggesting a potential cumulative impact from repeated doses. Most patients with hypophysitis experience generalized symptoms such headaches, lethargy, and malaise, which makes early identification challenging, especially in older persons. Confusion, fatigue, and a change in mental status are the more severe symptoms. ICI-related hypophysitis is uncommon compared to other explanations for visual symptoms brought on by disturbance of the optic system **(Kichloo *et al*., 2021)**.

2.4.4. Gastrointestinal and Hepatic

Both luminal gastrointestinal (GI) and hepatic side effects are frequently linked to immune checkpoint inhibitors. Although it is uncommon, immune-related pancreatitis has been reported in melanoma patients as well as those with solid tumors. It is challenging to distinguish between these disorders because the GI manifestations resemble idiopathic inflammatory bowel illness. A common and sometimes serious irAE is colitis. About one-third of individuals on ipilimumab treatment experience diarrhea, and 8–23% develop colitis. ICIs that target the PD-1 axis are less likely to cause GI irAEs, with colitis occurring in less than 4% of patients. Nivolumab, which has a 10–13% incidence of diarrhea, is an exception to this rule. After receiving ICI therapy, symptoms can begin anywhere from 11 days and 4 months later, with a typical onset time of 34 days. The most typical symptom of colitis is diarrhea. Other symptoms of colitis might include abdominal pain, emesis, fever, weight loss, and hematochezia. Hypokalemia and hyponatremia are two examples of possible electrolyte disorders. Changes in the gut flora may predispose patients to colitis in addition to a colitis' immunostimulatory mechanism. Hence, patients and healthcare professionals should exercise caution while starting antibiotic medication unless clearly required. A rare and perhaps dose-dependent consequence is colonic perforation **(Kichloo *et al*., 2021)**.

Hepatic transaminase levels are elevated in immune-related hepatitis without any accompanying symptoms, and it resembles an autoimmune-like drug-induced liver injury. Rarely, severe liver failure and hepatitis can ensue. Most frequently panlobular with a pattern of hepatocellular damage, ICI-associated hepatitis. Around 4% of individuals experience hepatic irAEs, which are less frequent than luminal irAEs. Patients taking ICI therapy for the treatment of hepatocellular carcinoma are more at risk. Serum transaminase and total bilirubin levels form the basis of the CTCAE grading system for hepatitis. Grades 2, 3, and 4 are assigned to transaminase values that are 3-5, 5-20, and 20x the upper limit of normal, respectively. Grades 2, 3, and 4 are assigned to total bilirubin concentrations that are 1.5–3, 3–10, and 10 times the upper limit of normal, respectively. With dual immune checkpoint inhibition, there is a dose-

dependent and higher likelihood of developing severe (grade 3 or 4) hepatitis. Typically, immune-related hepatitis develops 8 to 12 weeks following the start of ICI therapy **(Chhabra and Kennedy, 2021)**.

2.4.5. Renal

Due to the high incidence of kidney illness in cancer patients, renal irAEs have been documented in 2.2% of patients after receiving ICI therapy, however this number may be underreported. Up to 29% of patients are thought to be at risk for developing a low-grade irAE after receiving ICI therapy. However, hemodialysis-required high-grade acute renal damage is uncommon. Comparing combination ICI therapy to monotherapy, immune-related kidney damage is more likely. With anti-CTLA-4 therapy, the median time until the beginning of acute kidney injury is 2 months, and with ICIs that act on the PD-1 axis, the median time is 3 to 10 months. Similar cases of renal damage are seen with drugs that target the PD-1 axis. Oliguria, hematuria, or peripheral edema are symptoms. Although lupus nephritis and thrombotic microangiopathy have also been mentioned, acute interstitial nephritis is the most often documented cause of immune-related AKI. Proteinuria and the presence of anti-double-stranded DNA antibodies have both been mentioned in case reports **(Mamlouk *et al*., 2022)**.

2.4.6. Neurologic

In 6 to 12% of patients receiving ICI therapy, neurologic irAEs occur, and they are often of low degree. Headache, vertigo, and sensory impairment are examples of nonspecific symptoms of mild neurologic irAEs. A neurologist should be consulted for management of high-grade neurologic adverse events (AEs), which are uncommon and affect less than 1% of patients. These include central nervous system demyelination, myasthenia gravis, Guillain-Barre syndrome, Bell's palsy, meningitis, and encephalitis **(Chhabra and Kennedy, 2021)**.

2.4.6.1. Peripheral Nervous System

2.4.6.1.1. Myasthenia Gravis

The neuromuscular junction or muscle-specific kinases are the targets of pathologic antibodies in the neuromuscular transmission disorder myasthenia gravis. According to one series, two-thirds of incidences of myasthenia gravis after CPI therapy were in patients without a documented history of the disease or thymic cancer. These premorbid symptoms do exist in some cases, though. Variable levels of serum acetylcholine receptor antibody positivity exist. The connection with increased serum creatine kinase and clinical myositis is a characteristic that distinguishes myasthenia from CPI therapy. With electrodiagnostic findings of muscular

membrane irritability and myositis, this is highly unusual in non-iatrogenic myasthenia gravis but is present in more than 75% of patients with CPI-associated MG. Since a concomitant myocarditis may also develop in this population, cardiac enzymes, a cardiac MRI, and an early consultation with a cardiologist should all be taken into consideration when a suspicion exists. High morbidity and mortality rates are another crucial aspect of CPI-associated MG. In one series, over one-third of patients passed away from MG-specific reasons, and concurrent myocarditis increased mortality to 50% of patients in another group **(Harrison *et al*., 2021)**.

2.4.6.1.2. Myositis

Myositis, or muscular inflammation, can happen on its own or in conjunction with other irAEs such AIDP or myasthenia gravis to form an overlap syndrome. Dermatomyositis, polymyositis, and isolated hyperCKemia are a few possible manifestations. Concurrent myocarditis is a possibility and has been reported in as many as one-third of cases, as was mentioned above. Troponin I is advised for a precise myocarditis diagnosis, while troponin T increase may be elevated in neuromuscular diseases. Nearly half of the patients in one set of 19 individuals with CPI-associated myositis were characterized as having a severe case, and proximal myalgias and weakness were frequent. Pathologic analysis of muscle biopsies frequently indicated necrotic myositis. Early detection and care are essential for successful management of CPI-associated myositis because the consequences could be severe **(Harrison *et al*., 2021)**.

2.4.6.1.3. Neuropathy

Acute and chronic inflammatory demyelinating polyneuropathy (AIDP and CIDP, respectively) are the two conditions that affect the peripheral nerves most frequently that are related to CPI therapy. Cranial neuropathies, tiny fiber neuropathy, sensory ganglionopathy, and neuralgic amyotrophy are less frequently documented phenotypes. Additionally uncommon are plexopathies and isolated root inflammation. Over 50% of individuals have concurrent inflammatory disease that affects other organ systems. Over 60% of patients with some form of neurologic toxicity also had a component of neuropathy as part of the irAE, according to an analysis of 12 trials with ipilimumab or nivolumab. These neuropathies are frequently encountered along with other neurologic symptoms **(Harrison *et al*., 2021)**.

2.4.6.2. Central Nervous System

2.4.6.2.1. Central Demyelination

De novo CNS demyelination has been linked to CPI therapy. In patients who have already been diagnosed with MS, there is evidence that these medicines can cause exacerbations of the disease. Upon analysis of cases of newly diagnosed or relapsed multiple sclerosis in

patients receiving CPI treatment that were reported to the FDA, it was discovered that 57% of cases included patients who already had multiple sclerosis. The effects in these patients typically started to show up 29 days after the start of the medication and progressed quickly. Of the 14 patients in this series, two of them passed away from their relapse. It has also been noted that severe relapses can exacerbate in people with current MS who already have the relapsing-remitting condition. Nivolumab has been reported to cause florid multifocal CNS demyelination that is consistent with ADEM (acute demyelinating encephalomyelitis), with subsequent recovery with steroids and IVIG. One example of de novo demyelination was linked to improved responses of peripheral CD4+ T cells that are myelin-reactive, similar to controls who have MS without prior checkpoint inhibitor medication **(Harrison *et al*., 2021)**.

2.4.6.2.2. Meningitis/Encephaliitis

There have been numerous cases of aseptic meningitis recorded following CPI treatments. Although the exact incidence of these conditions is unknown, atezolizumab treatment resulted in the development of aseptic meningitis in 3 out of 29 patients in one institutional series. These patients have classic meningitis symptoms, including headache, photophobia, and nausea. Elevated opening pressure, lymphocytic pleocytosis, and negative results from viral investigations are frequently seen in cerebral spinal fluid testing. Brain parenchyma involvement is a symptom of encephalitis. Though cases of encephalitis linked to anti-Hu antibodies, GAD-65 encephalitis, and NMDA receptor antibodies have been found, the majority of documented cases are not linked to synaptic or paraneoplastic antibodies **(Harrison *et al*., 2021)**.

2.4.6.2.3. Vasculitis

Peripheral neuropathy, ischemic and hemorrhagic strokes, and rheumatological illnesses such as vasculitis and lupus-like syndromes should be viewed as the underlying causes in patients taking CPIs. 53 suspected vasculitis cases linked to CPI therapy were found in one systematic review. The bulk of these cases involved large or medium vessels. The CNS was affected in eight of the patients, four of which were classified as primary CNS angiitis, three of which were giant cell artieritis, one of which was isolated retinal vasculitis, and three of which had a specific vasculitis polyneuropathy. There were no reported vasculitis fatalities **(Harrison *et al*., 2021)**.

2.4.7. Rheumatologic

It can be difficult to identify rheumatologic IRAEs from other musculoskeletal complaints in cancer patients, because this patient population already exhibits a high baseline frequency of musculoskeletal symptoms. Arthralgia, inflammatory arthritis, rheumatoid arthritis-like disease, inflammatory myopathy, scleroderma, vasculitis, myalgias, and polymyalgia rheumatica are only a few of the rheumatologic problems that have been reported after ICI therapy. The ICIs that act on the PD-1 axis and have a tendency to manifest later than most other irAEs are more likely to cause these problems. Rheumatologic IRAEs have been documented to appear in a variety of ways, including sarcoidosis, giant cell arthritis, myositis, sicca syndrome, and systemic lupus erythematosus. Rarely, severe myositis that manifests as muscle weakness and increased creatine kinase (CK) can be deadly. Patients taking PD-1/PD-L1 inhibitors have been observed to experience this condition more frequently. As irreversible erosive joint destruction can happen within weeks, clinicians should have a strong suspicion for inflammatory arthritis and arrange rapid examination by a rheumatologist. **(Chhabra and Kennedy, 2021. Gumusay *et al*., 2022)**

2.4.8. Ocular

Rarely (less than 1% of patients) do patients receiving ICI therapy experience ocular irAEs. Its depending on the location of the eye afflicted, different ocular IRAEs can happen. Although uveitis, ulcerative keratitis, choroidal neovascularization, and orbital inflammation have also been noted, along with retinal choroidal disease, optic neuropathy, and various presentations of ocular inflammation like episcleritis, blepharitis, and orbitopathy (idiopathic or thyroid-induced orbitopathy), dry eyes are the most frequently reported irAE. The symptoms of patients can include impaired or distorted vision, alterations in color vision, blind spots, photophobia, eye pain, swollen eyelids, and proptosis. Uveitis may manifest as eye redness, and episcleritis may cause a red or purple staining of the eye. Along with extraocular IRAEs, ocular toxicity—particularly colitis—has been described **(Gumusay *et al*., 2022)**.

2.4.9. Pulmonary

Pneumonitis is a rare irAE, but when it does exist, it can be deadly and rapidly worsen. It occurs more frequently after PD-1 and PD-L1 medicines than after ipilimumab therapy, with the exception of atezolizumab. Initial symptoms may be non-specific and the median time to onset is 10–12 weeks after ICI therapy. Given the delayed onset and potentially fatal consequence, clinicians must always have a high degree of suspicion for immune-related pneumonitis. Dyspnea and cough are the most frequently seen initial signs **(Chhabra and Kennedy, 2021)**.

2.4.9.1. CTLA-4 Inhibitors

At the time of writing, the FDA has only approved ipilimumab as a CTLA-4 inhibitor. Pneumonitis of any grade occurs in 1.3% of patients treated with ipilimumab, while high-grade (grades 3 or 4) pneumonitis occurs in 0.3% of individuals treated with the drug. The most typical pattern of pneumonitis is OP, and the median interval between the start of treatment and the onset of the condition has been estimated to be around 2.3 months. Although pneumonitis is less frequent with CTLA-4 inhibitors than PD-1 or PD-L1 inhibitors, the mechanism underlying this difference is unknown. Compared to patients receiving treatment for renal cell cancer or non-small cell lung cancer, people receiving ipilimumab for melanoma experience pneumonitis at a rate that is roughly one-third lower. The existence of lung illness from smoking, as has been noted in other ILDs, may be one explanation for this **(Altan *et al.*, 2021)**.

2.4.9.2. PD-1 and PD-L1 Inhibitors

The PD-1 inhibitors nivolumab, pembrolizumab, and cemiplimab, as well as the PD-L1 inhibitors atezolizumab, avelumab, and durvalumab, will be covered in this section. In contrast to standard chemotherapy regimens, pneumonitis after PD-1 inhibition occurs up to three times more commonly in a variety of cancer types. Recent research indicates that the incidence of all-grade pneumonitis in clinical trials with PD-1 inhibitors is approximately 3%, with the majority of studies showing incidence rates of 3-5%. In clinical trials, PD-1 inhibitors had an incidence of high-grade (grade 3 or higher by CTCAE criteria) pneumonitis of 1–1.5%. However, the prevalence of pneumonitis appears to change amongst various tumor types. An indicator of future risk for the emergence of immunological checkpoint-related pneumonitis is the presence of preexisting fibrotic ILD. In one study, patients with non-small cell lung cancer (NSCLC) and minor baseline pulmonary fibrosis had a 28.6% incidence of PD-1-related pneumonitis compared to 5.8% of patients without fibrotic ILD, indicating that even mild baseline ILD may be associated with increased rates of pneumonitis. In this situation, ICI-related pneumonitis may worsen existing ILD or encourage the development of new illness. Similar to ipilimumab, smoking-related malignancies appear to have a greater prevalence of pneumonitis following PD-1 suppression. Smoking status was not linked to the incidence of pneumonitis in a case-control study of patients who experienced the condition after receiving PD-1 inhibitor therapy, although a history of COPD or lung irradiation was. nevertheless seems unlikely that the incidence of pneumonitis varies with the dosage of PD-1 inhibitors, indicating that irAEs are not directly related to these treatments in a dose-dependent manner. This supports our finding that

pneumonitis following PD-1/PD-L1 axis inhibition appears to be an atypical phenomenon. When individuals are treated outside of the carefully monitored environment of clinical trials, pneumonitis rates could be greater. Pneumonitis was the most frequent cause of therapy-related mortality, with a case fatality rate over 10%, according to an assessment of fatal immune checkpoint inhibitor toxicities from a WHO pharmacovigilance database. As one of the most sensitive organs to ionizing radiation, the lung, concurrent ICI and radiation therapy may increase the risk of pneumonitis due to overlapping risks for lung inflammation. The pneumonitis rate (G 1), which included pneumonitis from an irAE or secondary to radiation pneumonitis or as a result of a combination of both, was reported as 34% in a phase III randomized trial exploring durvalumab after concurrent chemoradiotherapy in stage III NSCLC, compared to 25% in the placebo arm. The most prevalent adverse event that resulted in the study regimen being discontinued was pneumonitis (4.8% of individuals receiving durvalumab and 2.6% of patients receiving placebo). In a contemporary investigation, ICI use in combination with chemotherapy and radiation had been linked to 8% of patients developing grade 3 pneumonitis. Pneumonitis is seen less commonly after PD-L1 inhibitor therapy than after PD-1 inhibitor therapy, according to recent studies. The total incidence of any-grade pneumonitis for avelumab in patients with advanced solid tumors, for instance, was roughly 1.2% in a pooled review of data from phase 1 and phase II trials. Likewise to this, Pillai et al. and Khunger et al. showed that NSCLC patients treated with PD-1 inhibitors experienced a greater incidence of any-grade pneumonitis than those treated with PD-L1 inhibitors (PD-1 vs. PD-L1: around 4% vs. approximately 2%). There are various qualifiers that can make these findings biased. With varied dosages of PD-1/PD-L1 inhibitors, both randomized and single-arm, open-label trials were included. Additionally, these trials' patient populations weren't always the same. For instance, while most trials involved patients who had already received treatment, some trials enrolled patients who had not, which may have an impact on how well the medication was tolerated. Furthermore, there is a dearth of information from randomized, controlled trials that compares the toxicity of PD-1 and PD-L1 inhibitors directly. Given that these treatments have been approved for new tumors, additional research is required to better understand the prevalence of pneumonitis **(Altan *et al.*, 2021)**.

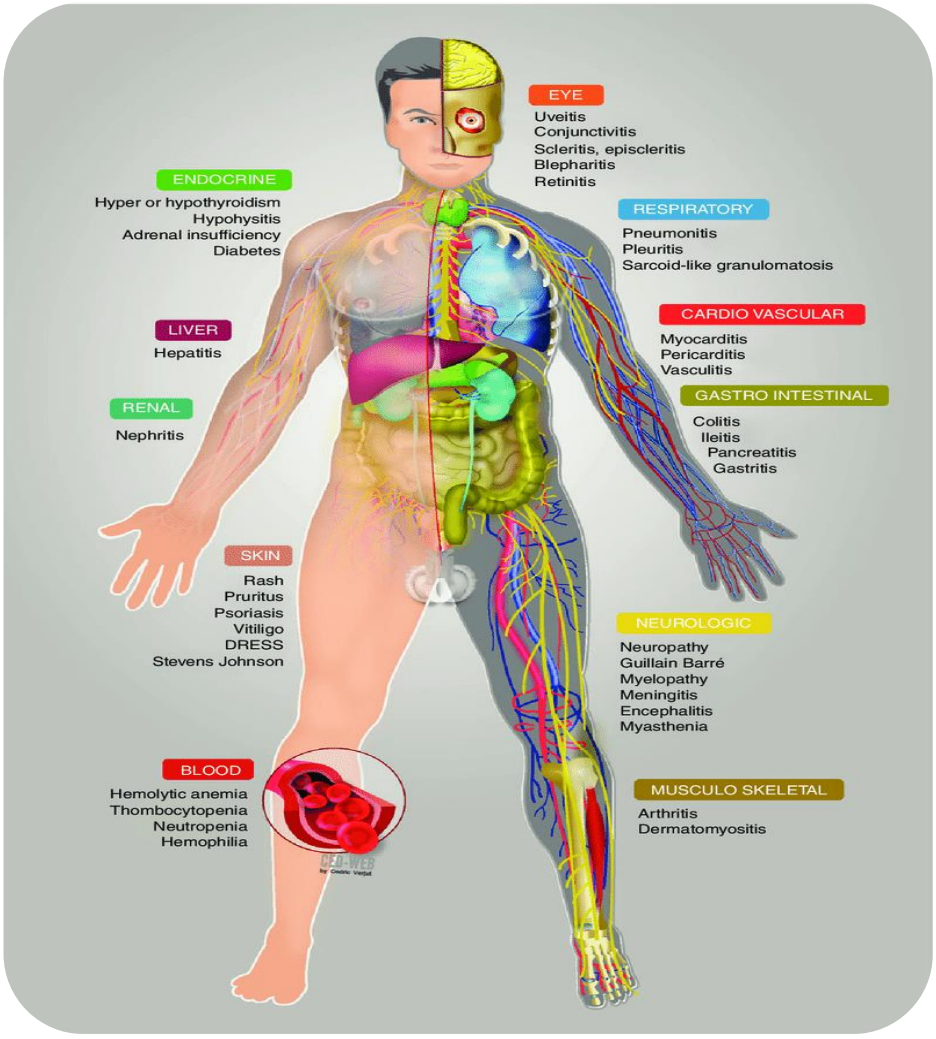

Figure 10. Spectrum of toxicity of immune checkpoint blockade agents **(Champiat *et al.*, 2016)**.

2.5. Monoclonal antibodies

2.5.1. Infusion Reactions

Chills, rigors, and autonomic instability, including hypotension and cardiovascular collapse, can be symptoms of infusion reactions (IRs), which are frequently linked to monoclonal antibody therapy. These may happen during antibody infusion or shortly after administration. Even though anaphylaxis typically manifests within minutes (immediate hypersensitivity), IRs often present within hours, making them difficult to distinguish from one another. Most frequently connected to trastuzumab and cetuximab, IRs are most frequently experienced with rituximab (up to 80% of individuals encounter one at some time during treatment). It's unfortunate that 10–30% of infusion responses can appear after the first infusion. Therefore, even if previous infusions have gone smoothly, monoclonal antibody infusion therapy should be administered in a monitored setting with access to resuscitation tools. With one fatality

reported among 1373 individuals participated in clinical studies, cetuximab carries a black-box warning indicating a 2-5% risk of severe infusion response **(Chhabra and Kennedy, 2022)**.

2.5.2. Cardiovascular

A potentially fatal side effect known as heart failure associated with trastuzumab toxicity occurs in 1–4% of individuals receiving this medication. The EGFR family member human epidermal growth factor receptor 2 (HER2), which is present in cardiac myocytes, is known to interfere with signaling. Trastuzumab is also thought to impede the process by which damaged myocytes are repaired. As little as two weeks after therapy begins, toxicity might happen. Risk assessment for patients who might get monotherapy is still challenging because trastuzumab had historically been used in combination with cardiotoxic anthracycline chemotherapy. Bevacizumab is related with reversible and temporary vascular toxicity that develops as a result of endothelial dysfunction and smooth muscle cell dysfunction and may cause venous and arterial thrombosis that affects numerous organ systems **(Chhabra and Kennedy, 2022)**.

2.5.3. Idiosyncratic and Life-Threatening

Steven's Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are examples of dermatologic toxicity that can be fatal when treated with rituximab. Bevacizumab has been linked to gastrointestinal perforation, necrotizing fasciitis, and poor wound healing. Bevacizumab therapy has also been linked to a few uncommon occurrences of thrombotic microangiopathy. More frequently than with other monoclonal antibodies, rituximab has been associated with rare but severe pulmonary toxicity, including ARDS, diffuse alveolar hemorrhage and bronchiolitis obliterans organizing pneumonia (BOOP). A distinctive property of alemtuzumab, a CD52 monoclonal antibody, is that it dramatically increases patients' susceptibility to systemic infections such Pneumocystis jiroveci, CMV, herpes, and EBV as well as T-cell depletion. Patients receiving alemtuzumab may be more susceptible to additional negative drug events if antimicrobial medications are used as preventative measures (e.g., trimethoprim-sulfamethoxizole, dapsone, and others) (figure 11) **(Chhabra and Kennedy, 2022)**.

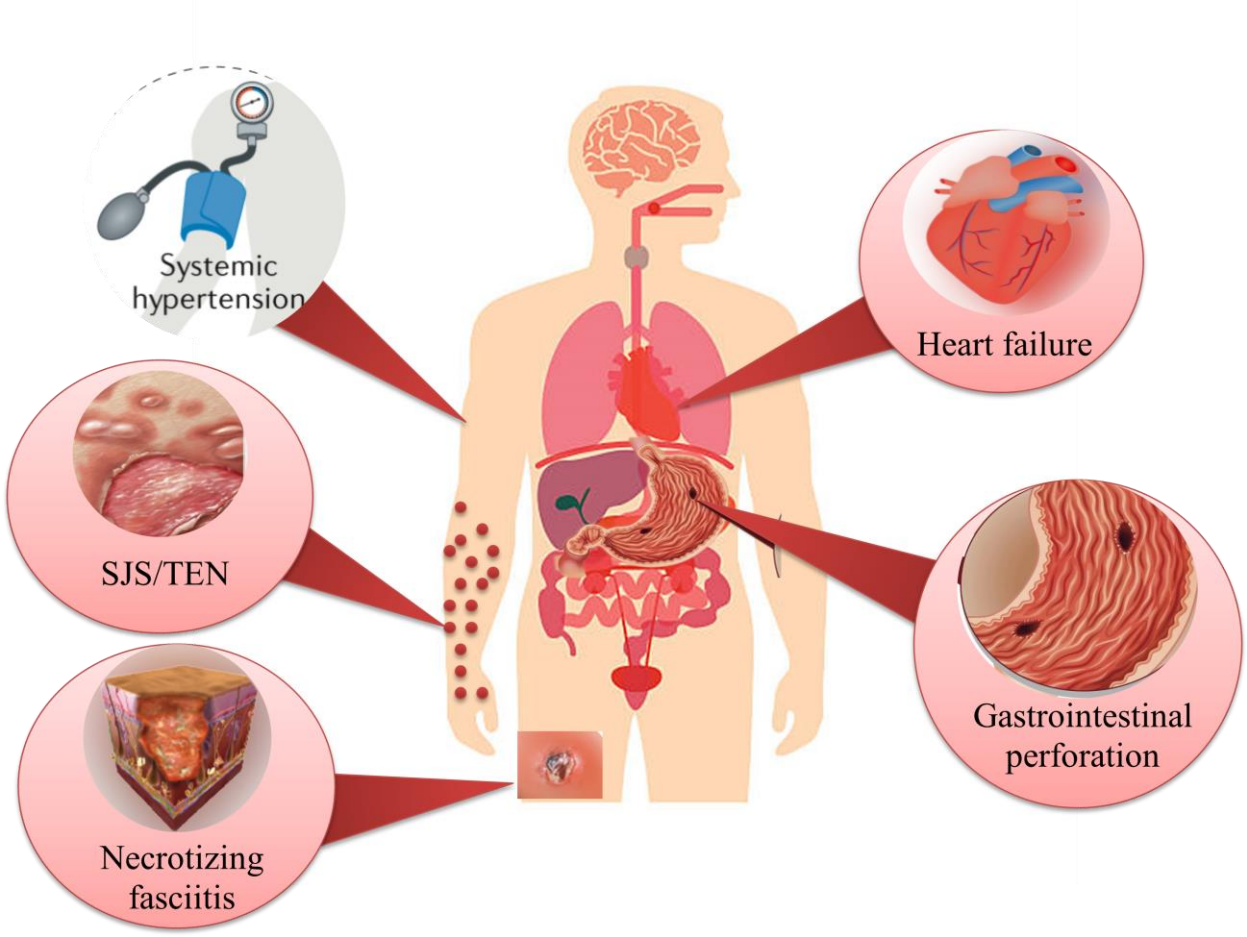

Figure 11. Various adverse effects of monoclonal antibodies therapy

2.6. Oncolytic Viruses

Currently, a broad spectrum of viruses are being researched for the treatment of cancer. The most prevalent delivery method for talimogene laherparepvec is intra-tumoral injection, while intraperitoneal and intravenous OVs are also being studied. Dosage schedules differ greatly. Clinical trials that have recently been published have not revealed any substantial safety or toxicity issues. Safety and toxicity concerns are anticipated to surface as more OVs go through clinical testing and more patients are investigated. Toxic consequences could arise from immune stimulation that is off-target and cell lysis. Investigations have also excluded participants with current viral infections and weakened immune systems. It's crucial to watch out for harmful effects because individuals with these illnesses might receive OVs in the future. Local responses are frequent but often minor at injection locations. 1–2% of patients have been reported to have cellulitis. Despite being injected directly into the tumor, the possibility of systemic effects following local injection has been highlighted by the regression of distal tumors from the injection site. The secondary effect of systemic immunostimulation is probably this. Both local and systemic delivery of OVs have been associated with minor influenza-like

symptoms, such as fevers and chills. Additional putative causal agents for negative consequences are cellular carriers of OVs. There are currently no particular treatment recommendations due to the scarcity of instances of serious toxicity. It is noteworthy that OVs created from herpes simplex virus type 1 (oHSV1) maintain the native thymidine kinase gene that aids in viral replication. The antiviral drug ganciclovir works to inhibit this, making it possible to treat severe HSV-based OV toxicity with this therapy. To our awareness, the medical literature is not currently reporting any cases of OV overdose. OV has not been reported to be transmitted from person to person. No instances of modified viruses recombining with wild-type viruses have been documented. In one study, lesions suggestive of herpetic infection later appeared in five patients receiving intralesional OV treatment for melanoma. By quantitative PCR, the lesions in four of the five patients tested negative for talimogene laherparepvec DNA, whereas the lesion in the fifth patient showed positive but the area had already had talimogene laherparepvac injections. In a different investigation, DNA from talimogene laherparepvec was found in three individuals with lesions that appeared to be of herpetic origin but were located far from the site of the original injection. None of these strains showed signs of infection. Live virus appears in injected lesions and is visible on the surface of lesions throughout treatment. Transmission is unlikely, though, if occlusive dressings are used properly, as no live virus has been found on the outside of dressings. Although it is not conceivable for OVs like oHSV to spontaneously transform into wild-type HSV, the emergence of compensatory mutations that jeopardize safety is possible but has not yet been reported (figure 12) **(Chhabra and Kennedy, 2022)**.

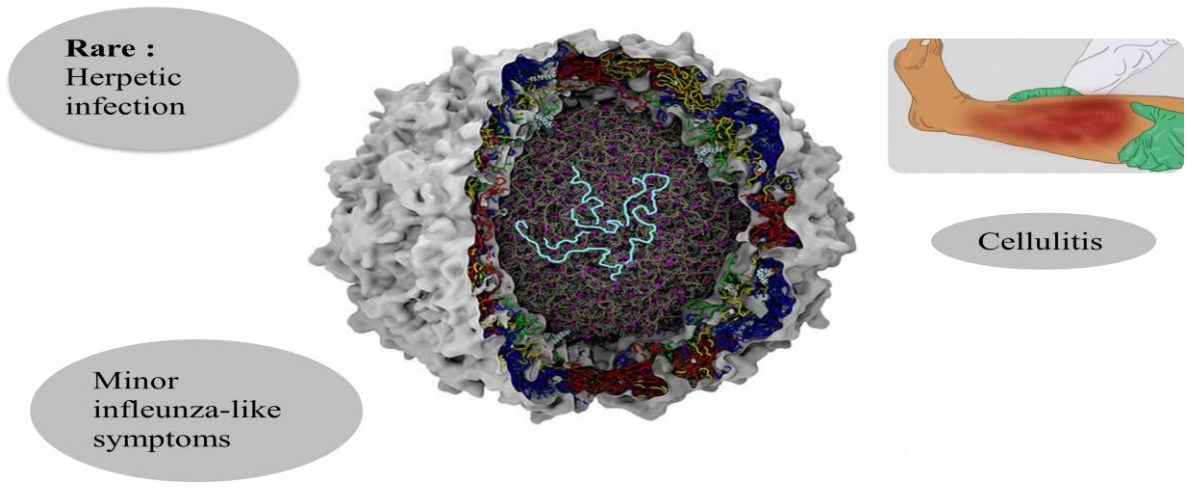

Figure 12. Certain toxicities of oncolytic viruse

CHAPTER III

Immunotherapy toxicities management

3. Immunotherapy toxicities management

3.1 Adoptive cellular therapy

3.1.1 Cytokine Release Syndrome

Any grade of CRS requires daily physical examinations and laboratory tests for patients who need close observation. Supportive care, anti-cytokine focused therapy, corticosteroids, and vasopressor support are some of the treatment options that vary depending on the severity of the toxicity. With 1-2 liters of intravenous fluids (IVF) boluses, vasodilatory hypotension can be treated, but vasopressors should be used as soon as possible. For grade 2 CRS and grade 3 or higher CRS, the IL-6 receptor blocking antibody tocilizumab is advised. Tocilizumab should be given with corticosteroids and a second dosage if CRS does not improve after receiving a single dose of the medication. Other medications such siltuximab, anakinra, and high-dose methylprednisone can be investigated in individuals with persistent or progressing CRS after receiving two doses of tocilizumab plus steroids, although a fresh wide infection workup is also advised. It is advised to use an initial dose of no more than 1 mg/kg of prednisone equivalent when using steroids to treat CRS, followed by a quick taper over a period of 7–10 days **(Ayers *et al*., 2022)**.

3.1.2. Cardiovascular

Corticosteroids or tocilizumab in situations of lymphocytic myocardial infiltration, as well as routine care for heart failure or dysrhythmias, may be used in the treatment of cardiovascular toxicity depending on the specific cause **(Montisci *et al*., 2021)**.

3.1.3. Gastrointestinal

The use of immunomodulator therapy may be necessary for severe refractory colitis, even if the majority of gastrointestinal damage is minor and self-limiting. Before starting to deliver budesonide locally to the colon in these immunosuppressed patients with possible infectious causes of colitis, a thorough workup is required. When administering antibiotics, common gastrointestinal pathogens should be the target, or a culture should be used if one is available. With the exception of severe toxicity, localized steroids are preferred to systemic ones. The reported time to resolution is four to six weeks **(Chhabra and Kennedy, 2022)**.

3.1.4. Neurologic

Due to its poorly known etiology and greater range of symptoms, management ICANS is more diverse in practice. Patients who experience neurologic toxicity after CAR T-cell therapy should be managed similarly to how CRS is managed, which includes close monitoring with

daily physical exams and laboratory tests. When possible, a lumbar puncture should be considered in addition to the routine infection workup, and a CT scan or MRI should be done to rule out any other acute neurologic processes. Subclinical electroencephalographic seizures should also be investigated with an electroencephalogram, according to reports. Tocilizumab has not been found to be beneficial in reducing neurologic symptoms, despite cytokine focused therapy showing significant efficacy in the treatment of CRS. Due to the fact that tocilizumab does not pass the blood-brain barrier, there is also a theoretical possibility that brief elevations in serum IL-6 concentrations after tocilizumab administration could exacerbate the neurotoxicity of CAR T-cell therapy. Contrarily, corticosteroids have proven effective in treating ICANS and continue to be the cornerstone of treatment. Levetiracetam is advised for the management of patients with seizures even if there is inadequate data to support the recommendation of preventive antiepileptics **(Ayers *et al*., 2022)**.

3.1.5. Pulmonary

Positive pressure breathing may be started as necessary, as well as correcting hypoxemia with more oxygen as a treatment option **(Brudno and Kochenderfer, 2016)**.

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3.1.6. Renal

Within 30 days, all patients who received RRT passed away. If a patient survives following RRT, it is unknown if they will need long-term RRT. ICU admission, prior stem cell transplantation, and grades 3–4CRS are specific risk factors for acute renal damage. For the acute kidney associated with CRS, no particular course of treatment is advised. The primary form of therapy is still supportive care, which may include renal replacement therapy when necessary **(Brudno and Kochenderfer, 2016)**.

3.1.7. Miscellaneous

Although persistent visual and auditory impairment was common, local application of corticosteroids has been helpful in mitigating ocular and ototoxicity. In one instance, intratympanic corticosteroids were used, and the hearing loss was completely resolved. In addition to vitiligo, cutaneous lymphocyte infiltration, superficial infections, and subsequent cutaneous malignancies, dermatological abnormalities are more frequent. In the first week or so following treatment, vitiligo, cutaneous lymphocyte infiltration, and dermatological infections appeared. Later, 5 months or more after therapy, secondary cutaneous cancers and epidermal hyperplasia appeared **(Chhabra and Kennedy, 2022)**.

3.2. Cancer vaccines

There have been some reports that certain cancer vaccination Sipuleucel-T, can cause stroke. Stabilizing the patient and completing the initial evaluation and assessment, including imaging and laboratory testing, within 60 minutes of the patient's arrival is the aim of the acute care of stroke patients.

Early on in the examination, hypoglycemia and hyperglycemia must be recognized and addressed. Both have the potential to cause symptoms that resemble those of an ischemic stroke and to exacerbate pre-existing neuronal ischemia. Insulin should be started in patients who have had a stroke and have hyperglycemia, while the administration of glucose in hypoglycemia results in a significant and rapid improvement.

Stroke and hyperthermia are rarely related, however it can worsen morbidity. When there is a fever (temperature >38° C), acetaminophen should be administered orally or intrarectally. When a patient has an established need for oxygen, more oxygen is advised.

It is still up in the air what blood pressure goals are ideal. Many patients arrive with high bloodpressure. American Stroke Association recommendations have reaffirmed the need for prudence while abruptly reducing blood pressure. Pharmacologically raising blood pressure may enhance flow across important stenoses in the tiny percentage of stroke patients who are somewhat hypotensive.

The best management practices involve continuous observation, early intervention as needed during the clinical course, eventual stroke recovery, and physical and occupational therapy **(Jauch *et al*., 2022)**.

3.3. Cytokines

3.3.1. IFN-a

Non-steroidal anti-inflammatory medicines can manage symptoms like nausea, vomiting, early satiety, anorexia, and weight loss after IFN. Severe exhaustion frequently necessitates lowering IFN dosage. Patients who have a temperature of more than 39°C for more than a day should be evaluated since it could be a sign of a systemic infection. Patients who have coughing, dyspnea, or other respiratory symptoms should also get a radiologic exam. Complete blood counts should be checked weekly during the induction phase, monthly for the first three months of the maintenance phase, and then every three months after that in order to manage myelosuppression, which could be controlled by stopping or lowering the dose. Antidepressants seem to work, as demonstrated by the prophylactic administration of paroxetine to 20 patients with malignant melanoma, which led to a reduction in significant depressive symptoms in 11%

of aroxetine-treated patients compared to 45% of placebo patients. Although prophylactic use of antidepressant medications can lower the risk of depression, patients with a history of severe depression are not allowed to receive IFN. However, it is also important to note that taking antidepressants may make depression symptoms worse **(Yang *et al.*, 2017)**.

3.3.2. IL-2

Vasopressors are able to treat hypotension even outside of the acute care unit because it is typically dose-related. Prior to the beginning of hypotension, individuals with CLS may benefit from early dopamine (1–5 g/kg/min) injection. This can help to preserve urine output and maintain organ perfusion. Clinical advice suggests upping the dose or adding phenylephrine hydrochloride if dopamine treatment fails to maintain blood pressure and organ perfusion. Adrenergic agonists can cause atrial arrhythmia, so patients using vasopressors should have their hearts monitored by telemetry. To lower the risk of sepsis, bacterial endocarditis, and catheter infection in patients with decreased neutrophil function, prophylactic antibiotics such as oxacillin, nafcillin, ciprofloxacin, or vancomycin can be given. In order to maximize the possible anticancer effects of IL-2, it is best to avoid administering glucocorticoids concurrently with it. Non-steroidal anti-inflammatory drugs have a higher risk for side effects. The side effects of IL-2, such as fever, hyperbilirubinemia, disorientation, and dyspnea, have been demonstrated to be relieved by these medications **(Yang *et al.*, 2017)**.

3.4. Immune checkpoint blockade

3.4.1. Cardiac

A systemic high-dose corticosteroid treatment must be started right away after stopping the ICI due to the risk of abrupt cardiac mortality. A gentle taper of oral prednisone or prednisolone in an outpatient setting after an initial dosage of 1-2 mg/kg/day of intravenous methylprednisolone is likely sufficient in the acute context. Up to 50% more patients with left ventricular dysfunction may recover with corticosteroid therapy. One gram of methylprednisolone per day as a dose increase should be taken into consideration for people who do not respond quickly to corticosteroids. Other immunosuppressive medications such tacrolimus, anti-thymocyte globulin (ATG), and mycophenolate mofetil, together with plasmapheresis, have been suggested for the treatment of steroid-refractory myocarditis, although there is currently a paucity of data to support their usage. It has also been suggested to use infliximab, a monoclonal antibody that targets the pro-inflammatory cytokine TNF-alpha, although this medication has the potential to hasten the start of new-onset congestive heart failure and so could exacerbate the cardiotoxicity caused by ICIs. For grade 1 toxicity and grade

2 or higher cardiac adverse events, ICI therapy should be permanently discontinued, in contrast to the majority of other irAEs **(Chhabra and Kennedy, 2021)**.

Table 01. Cardiac toxicities of immune checkpoint inhibitors **(Zarifa *et al*., 2021)**

Cardiac toxicity	Time to onset	Management
Myocarditis	2–32 weeks	High-dose corticosteroids (1 to 2 mg/kg of prednisone) initiated rapidly Mycophenolate, infliximab or antithymocyte globulin
Pericarditis/pericardial effision	6–15 weeks	
Arrhuthmia	2–8 weeks	Standard treatment can be followed per AHA/ACC guidelines
Hypertension	17–22 weeks	
Vascular disease	Within 26 weeks	
AHA/ACC American Heart Association/American College of Cardiology		

3.4.2. Dermatologic

Skin toxicity is often treated with topical medications and symptomatic therapy. In particular if vitiligo is present, patients should receive advice on photoprotection including clothing, helmets, and sunscreen to prevent sunburn. Consultation with a dermatologist should be sought if the diagnosis of a dermatologic irAE is in doubt. Skin biopsy may help with the diagnosis, especially if the rash has been present for a while or if it has persisted despite therapy. Topical corticosteroids, skin emollients, and antihistamines can treat grade 1 and 2 skin toxicity without delaying the ICI therapy schedule. The ICI treatment should be temporarily discontinued and a systemic corticosteroid should be taken into consideration for grade 1 and 2 skin toxicity that does not get better with this method. Systemic corticosteroids should be started in cases of uncommon grade 3 or 4 toxicity, and ICI therapy should be completely stopped **(Chhabra and Kennedy, 2021)**.

3.4.3. Endocrine

The mainstay of treatment for ICI-associated hypophysitis is physiologic hormone replacement under the guidance of an endocrinologist after a complete assessment of endocrine hormone failure. Prior to replacing the thyroid hormone, systemic high-dose steroids should be started to avert an adrenal crisis. While gonadal and thyroid function can recover in some

patients, adrenal recovery is uncommon. In individuals with hypophysitis, ICI treatment should be permanently stopped **(Chhabra and Kennedy, 2021)**.

3.4.4. Gastrointestinal and hepatic

With fluid and electrolyte replacement, grade 1 toxicity is primarily treated supportively. In situations of grade 2 colitis and grade 3 or 4 colitis, adding corticosteroids should be considered, and they should be started. A visit with a gastroenterologist and an endoscopic examination are advised in cases of grade 2 toxicity that do not improve with supportive care, as well as in the majority of cases of grade 3 and 4 toxicity if the diagnosis is unknown. Inflammatory changes involving exudates, granularity, and ulcerations are frequently visible during the course of an endoscopic examination. If there is a question about the diagnosis, an endoscopy can be used to perform a biopsy, although the risk of perforation must be considered. Systemic corticosteroids (1-2 mg/kg/day of methylprednisolone or its equivalent) should be started in grade 3 and 4 colitis in order to permanently stop the ICI therapy. If corticosteroids are ineffective after three to five days, an infliximab dose of five milligrams per kilogram has been administered satisfactorily. Colitis relapses frequently occur. Therefore, it is recommended to taper corticosteroids over a period of 6 to 8 weeks. Colitis or diarrhea cannot be prevented by prophylactic corticosteroids, according to research **(Kichloo *et al*., 2021)**.

At least one month should pass between corticosteroid dose reductions, or until grade 1 toxicity is reached. According to published case studies, mycophenolate mofetil is advised in circumstances where corticosteroids are ineffective. Anti-thymocyte globulin is one of the other medications that has been tried, however the evidence that is now available is only case reports. Because it may cause fulminant hepatitis, infliximab should be avoided **(Chhabra and Kennedy, 2021)**.

3.4.5. Renal

Steroids have historically been the predominant treatment for renal damage brought on by CPI. To comprehend innovative treatments, however, biomarkers for organ harm linked to CPI are required. Ipilimumab-treated patients have been found to have elevated levels of interleukin-17, and patients who don't respond to steroids after three days are started on infliximab at a dose of 5 mg/kg once every two weeks. Understanding innovative strategies might be furthered by staining renal tissue from individuals with irAEs for cytokines and T-cell subsets. A nephrology consultation, a lab test, and a urine analysis would be the standard treatment for AKI following CPI use. It is now obvious that determining if a patient has acute interstitial nephritis (AIN) vs a glomerular disease that may require more treatment than steroids would require an early renal

visit and a kidney sample. Steroids are the go-to therapy, with AIN beginning at 1 mg/kg and tapering over 1-2 months with careful monitoring. The use of biologics that target TNF-alpha suppression (infliximab) and IL-6 inhibitors (tocilizumab) in the treatment of glomerular disease are the most crucial information in this work. Relapse of ATIN is problematic and is linked to a worse prognosis for the kidneys. Oncologists and other experts are becoming more interested in using biologics that suppress TNF-alpha (infliximab) and IL-6 (tocilizumab), which target these two diseases. To guarantee improvement, it would be crucial to closely monitor creatinine every two weeks. Oncologists and transplant nephrologists must work closely together to prevent organ rejection in kidney transplant recipients. According to one case, moving from tacrolimus to sirolimus and taking more steroids while receiving immunotherapy may have helped to prevent organ rejection. higher immunosuppressive therapy prior to CPI infusion may reduce the likelihood of higher rejection **(Abdelrahim *et al*., 2021)**.

3.4.6. Neurologic

Table 02. Management of suspected neurological immune-related adverse effects (irAEs) **(Albarrán *et al*., 2022)**

Grade	**CTCAE**	**Management**
Grade 1	Mild symptoms No interference with function Symptoms not concerning to patient	Consider to withhold ICI Close monitoring for any progression If irAEs worsen or do not improve, consider permanent discontinuation
Grade 2	Moderate symptoms Cranial nerve involvement. Some interference with ADL. Symptoms concerning to patient	Withhold ICI If irAEs worsen or do not improve (going to grade 1), consider permanent discontinuation Start 0.5–1.0 mg kg−1 day−1 prednisolone equivalents PO or IV; if worsening symptoms, 1–2 mg kg−1 day−1 *Initial observation reasonable
Grade 3	Severe symptoms Limits self-care	Permanently discontinue ICI Start 1–2 mg kg−1 day−1 prednisolone equivalents PO or IV

Grade 4	Life-threatening consequences	Permanently discontinue ICI Start 2 mg/kg−1 /day−1 prednisolone equivalents PO or IV

CTCAE: Common Terminology Criteria for Adverse Events. ADL: activities of daily living. PO: per oral. IV: intravenous.

3.4.7. Rheumatologic

Steroid-resistant instances have been described and treated using disease-modifying anti-rheumatic medications or TNF-alpha inhibitors like infliximab, despite the fact that they are normally treated with prednisone. Therapy sessions can last a long period, and patients occasionally need ongoing care. Given the worry over organ-specific consequences that could cause considerable morbidity and mortality, it is also important to assess suspected immune-related vasculitis right away **(Chhabra and Kennedy, 2021)**.

3.4.8. Ocular

Ophthalmologists and other medical professionals must be alert to the signs of probable irAEs, have a high level of suspicion about them, and be cautious in spotting these ocular toxicities as soon as possible. Ocular treatment-related adverse events (irAEs) may appear to be no different from the cancer's direct consequences or its indirect sequelae, but it is important to identify and differentiate these irAEs. Management recommendations are based on case studies, case series, and consensus among experts. Topical corticosteroids and/or lubricants are used to treat mild ocular toxicity, while systemic corticosteroids may be needed for severe adverse effects. Depending on the degree of toxicity and the patient's response to treatment, each individual case should be assessed before deciding whether to continue or discontinue treatment. Specific recommendations with clinical practice guidelines have recently been released, based on data from a thorough systematic review, published medical literature, and expert consensus. Immunotherapy should generally be continued while being closely monitored for grade 1 effects, for grade 2 toxicity, therapy may be discontinued or scaled back. For grade 2 toxicity, therapy may be discontinued or scaled back. Treatment should be stopped and high-dose corticosteroids should be explored for toxicities of Grade 3 or higher. After a grade 3 toxicity, a rechallenge can be considered under very strict safety measures. In all grade 4 situations, permanent discontinuance should be taken into account **(Al-Zubidi *et al.*, 2021)**.

3.4.9. Pulmonary

Additional oxygen might be required. Grade 3 or 4 toxicity patients should be hospitalized, get professional advice, and be treated with high-dose systemic corticosteroid therapy. If the symptoms of patients with grade 2 toxicity worsen during an initial observation period of 3 to 6 hours, they should additionally receive systemic corticosteroids and be admitted to the hospital. Infliximab, mycophenolate mofetil, or cyclophosphamide therapy should be started if steroid resistance still exists after 48 hours as seen by a lack of clinical or radiologic improvement. When ICI therapy is resumed in patients with grade 1 or 2 pneumonitis, the condition may return. When thinking about restarting ICI therapy, patients and providers should be aware of this risk **(Verma *et al*., 2022)**.

3.5. Monoclonal antibodies

The only course of treatment for infusion responses is supportive, with caution taken to distinguish between immediate type 1 hypersensitivity reactions and respond accordingly (with, for example, antihistamines, epinephrine, corticosteroids, and bronchodilators).

If trastuzumab is stopped as soon as cardiac toxicity manifests, it may be possible to reverse the condition; nevertheless, if treatment is continued, irreversible damage may result. It is advised to regularly assess cardiovascular function when monitoring for toxicity.

Angiotensin-converting enzyme inhibitors (ACE-I), beta-blockers, and stopping the monoclonal antibody are the best therapy options. Although mAb therapy should be stopped if there are serious and potentially fatal side effects **(Chhabra and Kennedy, 2022)**.

Table 03. Side effects of some of monoclonal antibodies and their management **(Fernandez *et al*., 2020)**

Examples	**Adverse effects**	**Management strategies**
Anakinara Avelumab Ipilimimab Nivolumab Pembrolizumab Rituximab Tocilizumab Tofacitinib	Infusion reactions	Premedicate with acetaminophen and diphenhydramine 30 minutes before the first and the second infusions
	Serum sickness	Pulse methylpredisolone therapy
	Stevens-Johnson Syndrome/toxic endothelial necrolysis and vesiculobullous dermatitis	Discontinue therapy
	Rash (lichenoid, bullous,	Topical corticosteroids, systemic

	psorasiform, macular, morbiliform morphologies	steroids

3.6. Oncolytic Viruses

The handling of AEs brought on by OVs is not governed by any published guidelines in the literature because most of these viruses are still being studied in the clinic. The norm is to take preventative action. First, the hospital's clinical research unit must be able to use genetically modified organisms in order to use a modified contagious pathogen for OV administration. The medical team at the hospital have to take extra care to keep pathogens away from them. The oncologists should confirm that the patients have no major history of immunodeficiency, such as HIV or active B or C hepatitis, and are not using antiviral drugs, before suggesting a treatment or clinical trial with an OV. Utilizing acetaminophen as prophylaxis regularly throughout treatment can help avoid post-infusion reactions. Stopping anti-hypertensive medication 48 hours before and 48 hours after the infusion, as well as encouraging adequate oral hydration, can help prevent hypotension when receiving treatment with JX-594. Patients undergoing treatment are instructed to often wash their hands, refrain from sharing personal goods like cutlery and toiletries, and stay away from intimate encounters. When pustules form, the cutaneous lesions must be covered with a hermetic dressing until they have subsided, and the peri-oral lesions must be covered with a mask **(Cousin *et al*., 2018)**.

Conclusion

Conclusion

The immune system is boosted and efficient antitumor immunity is restored through immunotherapy, a revolutionary treatment. By employing a variety of tactics involving adoptive cellular therapy, cancer vaccines, cytokines, immune checkpoint inhibitors, monoclonal antibodies also oncolytic viruses, it is intended to end this system's tolerance to cancer cells and enable the patient's immune system to fight off his illness.

Despite of their long rich history, significant advancements over the past decades, and dedication to other conventional treatments through the treatment of numerous diseases and their distinction particularly in the treatment of cancer, these strategies have demonstrated a number of toxicities that may inconvenience the patient and occasionally pose a threat to his life. Nevertheless minimizing or stopping employed doses temporarily and thoroughly understanding the traits of each of these tactics and the potential outcomes of using them with follow-up and attentive patient monitoring, furthermore prescribing drugs to lower immunological reaction such as immunosuppressant and steroids and some lifestyle modifications can help these side effects to be avoided.

Models more similar to and as complex as the human immune system may be used in delivery tactics to make predictions about potential toxicities and side effects that are more precise. As a result, the path of immunotherapy has many difficulties and constraints, and additional study is needed **(Taefehshokr *et al*., 2022)**. Relevant investigations are concentrated on tailoring antigen selection, maximizing drug development and manufacturing, developing improved preclinical models, identifying trustworthy biomarkers of response, and using combinatorial treatment strategies to overcome immune evasion and antigen heterogeneity within and among the patient population in order to increase the therapeutic efficacy of immune-oncology **(Delucia and Lee, 2022)**

Given all of the aforementioned information, the therapist should carefully assess whether to recommend immunotherapy for a lengthy period of time. Researchers should simultaneously work to improve this crucial treatment by identifying more potent and less hazardous approaches to treat patients so that the theory of combination therapies, which leads us to a different area of research, can be examined and explored.

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Abstract

Considering the evolution and variety of diseases in recent decades, the immune system has attempted to resist and defend itself in various ways. However, the difficulty has made it challenging for researchers to try to find alternative treatment options, allowing immunotherapy to emerge far from conventional approaches. However, like with any medication, there are regrettably side effects, and in this overview, we focused on the immunotherapy's toxicity. According to many recent research conducted on this type of treatment that is based on strengthening the immune system through the appearance and variation of its working mechanisms such as checkpoint inhibitors, monoclonal antibodies, adoptive cellular therapy, oncolytic viruses and vaccines, patients' exposure to toxicity varies by person, depending on the type of immunotherapy where it can include internal organs such as heart, external organs such as skin and eyes. Since reducing the frequency of these symptoms presented a new obstacle, researchers were eager to manage this side effects with some drugs and therapeutic methods as we previously mentioned keeping it still being enhanced.

Keywords : Cancer immunotherapy, Immunotherapy, Toxicity, Immune system

Résumé

Compte tenu de l’évolution et l’émergence de nouvelles maladies au cours des dernières décennies, le système immunitaire a tenté de résister et de se défendre de diverses façons. Toutefois, il est difficile pour les chercheurs de trouver d'autres options de traitement, ce qui a permis à l'immunothérapie d'émerger, loin des approches conventionnelles. Cependant, comme pour tout médicament, il y a malheureusement des effets secondaires, et dans ce mémoire, nous nous sommes concentrés sur la toxicité de l’immunothérapie. De nombreuses travaux récents, menées sur ce type de traitement ont vu le jour, basées sur le renforcement du système immunitaire par l’apparition et la variation de plusieurs mécanismes moléculaires tels que les inhibiteurs de checkpoint, les anticorps monoclonaux, la thérapie cellulaire adoptive, virus oncolytiques et vaccins. L’exposition des patients à la toxicité varie selon la personne, selon le type d’immunothérapie, où elle peut inclure des organes internes tels que le cœur, les organes externes tels que la peau et les yeux. Cela dit, la réduction de la fréquence de ces symptômes a présenté un nouvel obstacle, les chercheurs sont donc désireux de gérer ces effets secondaires et de limiter tant que possible leur fréquence d’apparition chez les patients.

Mots clés : Immunothérapie du cancer, Immunothérapie, Toxicité, système immunitaire

ملخص

مع التنوع الذي شهده عالَم الأمراض في العقود الأخيرة حاولت العضوية المقاومة والدفاع عن الذات بشتى الطرق لكن ولصعوبة الأمر جعلت الباحثين يحاولون ايجاد طرق أخرى للعلاج مما سمح للعلاج المناعي بالبروز بشكل جيد بعيدا عن الطرق التقليدية لكن مع الأسف لا يخلو كأي علاج آخر من ظهور أعراض ثانوية وهذا ما سلطنا الضوء عليه في هذه الأطروحة سميّة العلاج المناعي. بناءا على العديد من الأبحاث الحديثة التي أجريت على هذا النوع من العلاج الذي يرتكز على تعزيز جهاز المناعة من خلال ظهور واختلاف آليات عمله مثل مثبطات نقاط التفتيش، الأجسام المضادة أحادية النسيلة، العلاج الخلوي بالتبني، فيروسات انحلال الأورام واللقاح فإن نسبة تعرض المرضى للسميّة تختلف باختلاف الشخص ،نوع العلاج المناعي حيث بإمكانها أن تشمل الأعضاء الداخلية مثل القلب والأعضاء الخارجية كالجلد والعينين. مما شكل تحديا جديدا للباحثين لتقليل نسبة ظهور هذه الأعراض لذلك حرصوا على إدارة خطة العلاج ببعض الأدوية والطرق الإستشفائية كما وضحنا سابقا مما جعله لا يزال قيد التحسين.

الكلمات المفتاحية : العلاج المناعي للسرطان، العلاج المناعي، السميّة، الجهاز المناعي