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Immune-Related Adverse Events Secondary to Cancer Immunotherapy: Reshaping Cancer Management

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Abstract. Developments in the fight against cancer have been slowly progressing in the last few decades. However, recent discoveries in cancer therapy involving inhibition of negative immune regulation have shown promise. This review explores the role of immunotherapy in managing cancer. The key accomplishments to date, physiological aspects of immunotherapy, current challenges as well as future outlook will be discussed. Traditionally, cancer has been managed using surgery, radiation therapy, and chemotherapy. Despite controlling the growth of tumors, some patients experience tumor recurrences. In that case, immunotherapy offers an effective solution for specifically targeting and killing cancer cells and decreasing the rate of tumor relapse. The use of immunotherapy leads to autoimmune toxicities, which can affect multiple organ systems and are referred to as immune-related adverse events (irAE). In this review, we discuss the different irAE since recognizing such systemic toxicities would help in cancer management. Immunotherapy provides hope to fight a disease that has been stealing lives and offers an acceptable level of cancer management against different malignancies. However, given that cancer is a complicated process, researchers continue to gain more understanding with additional trials. Possibly, the future will offer a permanent effective therapeutic approach against different cancers.

Keywords: Immunotherapy, Immune-related adverse events, Immune checkpoint inhibitors, CAR T cells, Cancer management

Introduction

Globally, cancer is a problem that causes the death of over eight million people annually (Ferlay et al., 2019). According to recent reports by the International Agency for Research on Cancer (IARC), 7.6 million people died from cancer from different parts of the world. The susceptibility to cancer development is higher in developing countries, where IARC reports that cancer is the reason behind 63% of deaths (Basu et al., 2019). Cancer occurs as a multifactorial disorder that involves complex genome modifications resulting from the interactions between a host and their environment. This manifests as an uncontrollable and abnormal growth of cells, causing physiologic dysfunction. In addition, cancerous cells employ several mechanisms to evade apoptosis. This uncontrolled cell growth accompanied by decreased cell death results in the formation of a tissue mass called tumor (Sharma, Boise, & Shanmugam, 2019).

The hallmarks of cancer include evasion of apoptosis, cellular irresponsiveness to cell division signals, ability to penetrate other normal cells, independence of cells from growth signals, and uncontrollable replication. As a result, these factors create a microclimate that nurtures the development of benign tumors through the dysregulation of some regulatory proteins. The resultant extracellular environment also facilitates cancer development (Hanahan & Weinberg, 2011).

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At its onset, cancer appears as a tumor that invades other tissues, and is associated with organ dysfunction. For instance, lung cancer patients experience chronic coughs and loss of breath. Cancer symptoms vary among patients, which makes early cancer diagnosis difficult. The progression of the disease leads to weight loss, enlarged organs, and fatigue (Board, 2021). Importantly, doctors identify different cancers based on the type of tumor cells. The common types of cancer include blastoma, carcinoma, germ cell tumor, sarcoma, leukemia, and lymphoma. Often, researchers associate cancer development with factors like radiation exposure, smoking, environmental pollutants, obesity, and excessive alcohol consumption (Institute, 2015, 2021). Before the 1950s, surgery was the only tool to treat cancer (Das, 2012). However, in the 1960s, radiation therapy was introduced to control the spread of the disease. After years of observation, researchers realized that radiation therapy alone is ineffective in cancer treatment. This observation led to the development of a combined approach using drugs, immune therapies, and biological molecules (Cesano, 2015). Unfortunately, none of the available cancer therapy options have demonstrated acceptable efficacy in increasing patient survival or reducing mortality rates.

Immunotherapy in Cancer Treatment

The introduction of immunotherapy in cancer treatment changed the treatment paradigm, where the new focus became improving antitumor immune system responses. More so, as technologies improve, researchers aim to reduce the off-target effects of the treatments that destroy cancer cells, like chemotherapy. During cancer treatment, immunotherapy agents replicate natural immune mechanisms to attack cancerous cells, which is why this method is considered promising and strategic in treating different cancers (Emens & Middleton, 2015). With the limited efficacy of traditional cancer treatment options like chemotherapy, surgery, and radiation, researchers had to find more effective means for cancer management. One of the main challenges of traditional therapies, is their inability to control the damage to normal body cells, which exposes patients to further suffering. Often as a result, the immune system is negatively impacted during cancer therapy, further hampering the recovery process (Wargo et al., 2015). This challenge paved the way for the discovery of immunotherapy as a new alternative for cancer treatment. Immunotherapy involves training the patient's immune system to attack cancer cells. Often, immunotherapy uses particular components of an individual's immune system to fight cancer (Liu & Wu, 2019). As a result, it boosts the hosts' natural defenses, thus enabling it to overcome the immune evasion and immune suppression caused by cancerous cells (Beatty & Gladney, 2015). This process involves the generation of genetically modified immune components which replicate the natural immune system aiming to restore its function or improve it (Liu & Wu, 2019).

In the 1990s, the concept of cancer immune surveillance gained widespread acceptance, due to evidence generated from multiple animal tumor models (Kim, Emi, & Tanabe, 2007). Cancer immunoediting is a dynamic process implemented in three phases: elimination, equilibrium and escape. During the elimination phase, cancerous cells are detected and subsequently eliminated by the immune system. In the equilibrium phase, elimination of transformed cells results in immune selection and immune sculpting. The latterinduces tumor variants,decreases immunogenicity by becoming resistant to immune effector cells. Eventually, cancerous cells mutate to avoid detection by the immune system, and secrete a variety of factors that inhibit the initiation of an immune response (Kim et al., 2007). This creates the perfect environment for tumor development in the escape phase. Natural immunity controls the propagation of cancerous cells. In particular, during an innate immune response, cancer killers cells, including CD56+, CD3- and CD16+ natural killer (NK) cells, recognize and then eliminate tumor cells (Kim et al., 2007; Wu, Fu, Jiang, & Shao, 2020).

The body's immune system response against cancer is a complex process delivered in three phases: innate immune response, antigen-specific T-cell activation, and tumor cell lysis (Corrales et al., 2017). During the innate immune response, newly transformed cells are eliminated by granulocytes and macrophages. Dendritic cells and macrophages possess the capability to process and internalize tumor cells in order to present tumor antigens to effector cells, in the context of class II major histocompatibility complex (MHC-II) molecules (Duan & Luo, 2021). Dendritic cells then migrate to the lymph nodes where they interact with the naïve T-lymphocytes. This interaction generates specific T-cells called CD8+ T-lymphocytes. These CD8+ T cells can recognize tumor antigens on the surface of cancer cells and affect their lysis. Thus, the last step involves the migration of CD8+ T-lymphocytes towards tumor sites, where they kill cancerous cells by producing cytolytic molecules like perforin and granzyme B (Hochweller et al., 2010).

During perforin action, granzymes move into the cytoplasm of the cancerous cells, where serine protease triggers cysteine proteases inducing apoptosis. Similarly, the CD8+ T-cells can express FAS-ligand proteins (CD95L/ApolL) on their surface, which bind with FAS molecules (CD95L/ApolL) that are expressed on the targeted cancer cells (Wada et al., 2007). The death domain of the FAS molecule translocates in the cancer cells, leading to the recruitment of both procaspases 10 and 8. This is an alternative pathway for mediating apoptosis in cancerous cells. In light of this discovery, researchers have explored different strategies to reinforce the responses of the immune system against cancer development. Significant focus has been directed towards T-lymphocytes, which can identify tumor antigens and attack them to stop tumor growth. These approaches include the modification of T-cell and tumor microenvironment to alleviate stimuli that can trigger T-cell anergy (Saibil & Ohashi, 2020).

Targeting a patient's immune system is an effective strategy for cancer prevention and therapy. A patient's immunity can be targeted using activated autologous peripheral-blood mononuclear cells, in a therapy such as sipuleucel-T. In 2010, the Food and Drug Administration (FDA) in the United States approved the sipuleucel-T vaccine for the treatment of prostate cancer (Kantoff et al., 2010). While such developments show a lot of promise in the treatment of cancer, the development of effective cancer treatment by boosting the immune system has been slow and cautious. This is because cancerous cells employ a number of mechanisms to subvert an immune attack (Maciejko, Smalley, & Goldman, 2017).

Today, oncologists can use any of the immunotherapy types in clinical practice, including T-cell therapy, non-specific immunotherapies, monoclonal antibodies, oncolytic virus therapy, and cancer vaccines.

Adoptive T-Cell Therapy

Adoptive T cell therapy, or T-cell transfer therapy is a type of immunotherapy that makes one's own immune cells better able to attack tumors. There are two main types of T-cell transfer therapy: tumor-infiltrating lymphocytes (or TIL) therapy and chimeric antigen receptor (CAR T) cell therapy.

Tumor-Infiltrating Lymphocytes (TIL)

TIL therapy uses T cells called tumor-infiltrating lymphocytes which have been selected for enhanced reactivity to the patient's tumor. These selected T cells are then expanded *in vivo* and transferred back to the patient. The rationale for TIL therapy is to selectively expand T cells that have shown the propensity to react with the tumor and enhance the anti-tumor immune response (June, 2007).

Chimeric Antigen Receptor (CAR T) Cell Therapy

CAR T cell therapy has revolutionized cancer therapy as it has produced remarkably effective and durable clinical responses. CARs are engineered synthetic receptors that function to sensitize lymphocytes, most commonly T cells, to recognize and eliminate cells expressing

a specific target antigen. Binding of CAR T cells to target antigens expressed on tumor cells is independent from the MHC receptor, resulting in vigorous T cell activation and powerful anti-tumor responses. The success of anti-CD19 CAR T cell therapy against B cell malignancies resulted in its approval by the FDA in 2017. However, there are major limitations to CAR T cell therapy that must still be addressed. These include CAR T cell-associated toxicities, limited efficacy against solid tumors, developed resistance to the therapy, antigen escape, limited persistence, poor trafficking and tumor infiltration, and the immunosuppressive microenvironment (Sterner & Sterner, 2021).

Lately, engineered T cells like the CAR T cells have attracted the attention of researchers, and their clinical success have led to FDA approvals. Thesecells are isolated from a patient's blood to be genetically modified so that they can express CARs specific to the antigen in cancer tumor cells. After adequate trials, the engineered CAR T cells are infused back to the patient (Yee et al., 2002). When injected into a patient, these cells work by recognizing the targeted cancer antigen in tumors to induce cellular death. The advantage of the CAR T cell therapy is that it is administered as a one-time solution because these cells maintain their activity for over ten years after injection (Monette et al., 2016).

Non-Specific Immunotherapies

Non-specific immunotherapies are therapies that non-specifically stimulate the immune system in order to overcome cancer-mediated immunosuppression. There are mainly two types of agents used as non-specific immunotherapeutic agents (Tur & Barth, 2011):

Bacillus Calmette-Guerin (BCG)

The most effective intravesical nonspecific immunotherapeutic agent. The proposed antitumor mechanism of BCG involves activation of the immune system and the promotion of a local acute nonspecific inflammation. Immune cell activation in response to BCG is mediated by a family of transmembrane recognition receptors called Toll-like receptors (TLRs). BCG-induced inflammation facilitates the infiltration of a broad range of immune cells and the activation of pro-inflammatory cytokines such as interleukin-1 (IL-1), interleukin-6, and tumor necrosis factor-alpha (TNF-α) (Tur & Barth, 2011).

Cytokines

The antitumor activity of cytokines is mediated by one of two general mechanisms: first, a direct antitumor effect, and second, indirect enhancement of the antitumor immune response. Cytokine-activated lymphocytes and their secretory products such as interferon-gamma and tumor necrosis factors may contribute to the lysis of tumor cells *in vivo*. In humans, IL-2 and interferon-α2b are approved for the treatment of advanced melanoma and for the use in adjuvant therapy (Tur & Barth, 2011).

Cytokine interferon-α was approved by the FDA for the treatment of hairy cell leukemia in 1986. Treatment with interferon-α caused some patients to manifest partial remission. This treatment was later substituted in 1998 by recombinant IL-2, an immunotherapy technique authorized by the FDA for the treatment of metastatic renal and melanoma cancers (Oettgen, 1977). While IL-2 caused complete responses, it required high dosage, which exposed patients to complications like vascular leak syndrome (Oettgen, 1977).

Cytokines like lymphokines, interferons, chemokines, and monokines serve as immune modulators produced by the body's immune system (Conlon, Miljkovic, & Waldmann, 2019). Cytokines have different roles such as regulating inflammation and immunity. The development of recombinant DNA technology complemented cytokine treatments. For instance, recombinant interferon- α (IFN-α) has been used since its discovery in 1986 to treat cancer (Conlon et al., 2019). This cytokine targets oncogene expression and tumor growth in patients. Therefore, as an immunotherapy technique, it is perceived as ideal as an adjuvant in various treatment approaches such as cancer vaccines. Similarly, interleukins produced by

CD4+ helper T-cells activate and suppress CD8+ cytotoxic natural killer (NK) cells, CD8+ T-cells, and macrophages. Notably, amongst all the interleukins, IL-2 and recombinant IL-2 are often used in immunotherapy strategies for cancer. In particular, the recombinant IL-2 technology is extensively used because it enhances antitumor activities within NK cells and CD8+ T cells (Jiang, Zhou, & Ren, 2016).

Monoclonal Antibodies

Researchers have been using monoclonal antibodies (mABs) for the treatment of different cancers since their approval by the FDA in 1997. In particular, mABs like Rituximab that target the protein CD20 have been extensively used for the treatment of prostate cancer, neuroblastoma, and Hodgkin's lymphoma. Rituximab binds to tumor antigens causing antibody dependent cell-mediated cytotoxicity (ADCC) (Leget & Czuczman, 1998). However, some mABs such as catumaxomab are bispecific, which enable them to crosslink with different tumor antigens and retain their ability to activate immune effector againstcancer (Linke, Klein, & Seimetz, 2010). This treatment is mostly used for patients whose tumors express epithelial cell adhesion molecules (EPCAM), particularly CD3. I-tositumomab and Y-ibritumamabtrixetan are some of the mABs with radio nucleotides that recognize targets like CD20. These antibodies reduce the toxicity of cancer drug administration by targeting specific cells (Jacene, Filice, Kasecamp, & Wahl, 2007).

The application of monoclonal antibodies during cancer treatment provides the body with antibodies similar to those produced by the immune system. However, monoclonal antibodies target specific tumor antigens on the surface of cancer cells (Scott, Allison, & Wolchok, 2012). Presently, most of the widely used immunotherapies have monoclonal antibodies, which are also called checkpoint inhibitors. Tumor cells can evade destruction by the immune system by triggering immune checkpoint receptors that engage with T cells to inhibit T-lymphocyte function (Himmel, Saibil, & Saltman, 2020). Immune checkpoint inhibitors (ICIs) are monoclonal antibodies that prevent this immunosuppression by blocking the engagement of these checkpoint molecules, thereby reinvigorating the anti-tumor immune response.

Cell-Based Immunotherapies

Cell-based immunotherapies like adoptive T-cell therapy have intrinsic antitumor capabilities (Tunger et al., 2019). Often, this form of treatment is used alongside with other infusions of allogenic T-cells to enhance antitumor activities. Tumor-infiltrating lymphocytes (TILs) react towards epitopes and shared neoantigens to target and kill cancer cells. Some of the known tumor-specific antigens comprise antigens from cancer testis, mutant proteins, tissue differentiation proteins, viral and oncogenic antigens (Tunger et al., 2019). The current therapeutic approach consists of *ex vivo* expansion of TIL from resected tumor material and adoptive transfer into the patient following a lymphodepleting preparative regimen and administration of IL-2 (Perica, Varela, Oelke, & Schneck, 2015). In addition, cell-based immunotherapy may often involve genetic engineering to reduce toxicity and maximize the efficacy of immunotherapies. Peripheral blood T cells can also be isolated and genetically modified *in vitro* to express T cell receptors (TCRs) that target specific tumor antigens for the use of adoptive cell therapy. With the use of this method, large pools of tumor specific T cells can be generated (Yee et al., 2002). In this direction, a personalized technique was developed a decade ago to identify gene mutations in different cancerous tumors via exome sequencing (Shindo et al., 2019).

Oncolytic Virus Therapy

An oncolytic virus is a virus that infects and lyses cancer cells but not normal cells. Oncolytic viruses can occur naturally or can be made in the laboratory by modifying natural

viruses. Today, adenoviruses, herpes viruses, measles viruses, coxsackie viruses, and polioviruses, among others, are some of the oncolytic viruses under preclinical and clinical development for cancer therapy. Adding different immunomodulatory transgenes to the viruses is one strategy gaining momentum in order to develop high-efficacy oncolytic viruses. With this approach, immunostimulatory molecules can be produced at the tumor site with reduced systemic side effects. Preclinical studies suggest that additive or synergistic effects can be obtained by combining oncolytic viruses with conventional treatments such as radiotherapy, chemotherapy and ICIs (Hemminki, Dos Santos, & Hemminki, 2020).

Cancer Vaccines

Therapeutic cancer vaccines such as Sipleucel-T have been discussed previously in this review. Presently, prophylactic cancer vaccines to prevent tumor development are rare, and most of the available ones are being investigated to determine their potency and side effects. With successful trials, prophylactic cancer vaccines will provide an effective mean to expose patient's immune system to particular tumor antigens (Curiel, 2013). This interaction will cause the immune system to destroy cancer antigens with the assistance of interleukins and interferons.

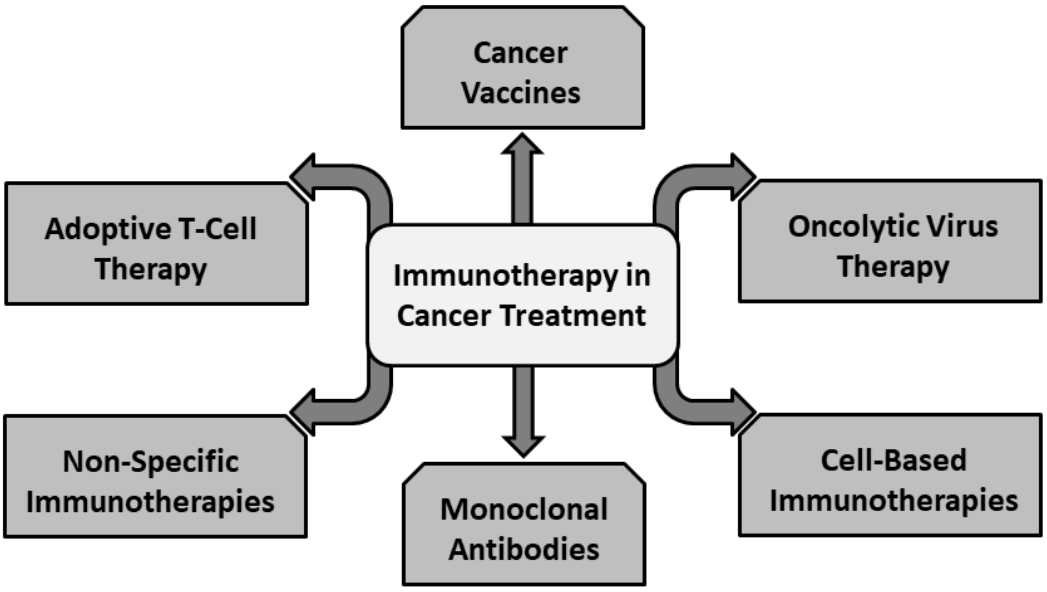

Figure 1. Cancer treatment using immunotherapy: adoptive t-cell therapy, non-specific immunotherapies, monoclonal antibodies, cell-based immunotherapies, oncolytic virus therapy and cancer vaccines

Immune-Related Adverse Events

irAEs are a subset of adverse effects of ICIs that are similar to autoimmune reactions. irAEs affect nearly every organ in the body, with the skin, gastrointestinal tract, lung, and endocrine, musculoskeletal, and other systems being the most typically affected (Zhou et al., 2020). Across disease sites, patients who experience irAEs while on therapy with anti-programmed cell death (anti-PD-1) and anti-programmed cell death ligand 1 (anti-PD-L1) antibodies have been documented to experience improved outcomes as measured by overall response rate (ORR), progression-free survival (PFS) and overall survival (OS) (Ishihara et al., 2019; Ricciuti et al., 2019; Toi et al., 2019). However, in patients treated with anti-cytotoxic T-lymphocyte-associated protein 4 (anti-CTLA-4) antibodies, this association has been less uniform (Ahn et al., 2019; Judd et al., 2017; Ksienski et al., 2019; Rogado et al., 2019). In

general, irAEs are thought to signal a better response to ICI therapy since they arise as a result of immunological activation. However, the predictive potential of irAEs to the development of anti-tumor immune response is debatable (S. Das & Johnson, 2019).

Diabetes

ICI-induced diabetes mellitus (ICIDM) has been reported with an incidence of 0.9% to 1.4% in two large case series (Kotwal, Haddox, Block, & Kudva, 2019; Stamatouli et al., 2018). When considering patients treated with a PD-1 inhibitor (pembrolizumab and nivolumab), this percentage increases to 1.8%, as no cases of ICIDM have been described with a CTLA-4 inhibitor (ipilimumab) (Kotwal et al., 2019). Marchand *et al.* recently categorized ICIDM into four distinct entities: (a) acute diabetes with autoimmune destruction of beta cells, with most cases presenting as fulminant diabetes; (b) complication of autoimmune ICI-induced pancreatitis; (c) type 2 diabetes mellitus (T2DM) phenotype-like presentation or decompensation of previously known T2DM; and (d) diabetes following autoimmune lipoatrophy (Marchand et al., 2019).

The relationship between diabetes and ICIs has been widely studied during the past two decades, and a lot of progress has been made. However, the exact pathophysiological defects behind ICIDM remain largely unknown. Preclinical studies on mice have shown that the PD-1/PD-L1 pathway is important for the development of autoimmune diabetes. In a prediabetic non-obese diabetic (NOD) mouse model, Ansari *et al.* demonstrated that PD-1 or PD-L1 blockade rapidly accelerated diabetes. On another hand, CTLA-4 blockade induced disease only in neonates (Ansari et al., 2003). This study was pivotal in highlighting the important role of the PD-1/PD-L1 pathway in the regulation of T-cell activation and tolerance.

The mechanism by which PD-1/PD-L1 pathway facilitates diabetes is not yet completely understood. Loss of PD-1 (but not PD-L1) resulted in increased cell numbers of antigen-specific CD4+ T cells levels in the pancreas and spleen, increased expression of several chemokine receptors, and transition from peri-insulitis to destructive insulitis in NOD mice (Pauken, Jenkins, Azuma, & Fife, 2013). Therefore, it appears that PD-1 regulates islet-reactive CD4+ T cells by inhibiting their proliferation and limiting pancreas infiltration (Pauken et al., 2013). However, another research study demonstrated that the total number of T cells was not significantly altered between non-diabetic wild-type, diabetic and PD-1 transgenic mice. Instead, the study reported that change in T cell function, and a noticeable reduction in forkhead box protein P3 (FoxP3) expression in the pancreas and spleen of diabetic subjects in comparison to wild-type and PD-1 transgenic mice (Won et al., 2010).

In ICIDM, the inhibition of PD-1 through PD-1 or PD-L1 pharmacological blockade could theoretically lead to increased infiltration and destruction of pancreatic beta cells by activated autoreactive T cells. However, it is unclear whether PD-1 inhibition leads to decreased proliferation and/or function of regulatory T cells (Treg) cells, followed by activation of autoreactive islet-specific T-cells, or if PD-1 inhibition directly removes the inhibitory pathway, thus activating these autoreactive T-cells (Zhang et al., 2020).

Future investigations should aim at elucidating the specific mechanisms of T cell activation, the function of different subtypes of PD-1-expressing T cells and the interaction between immune cell subtypes (Kapke et al., 2017). Another area of research would be to determine new biomarkers for susceptibility to ICIDM. Such biomarkers may help predict ICIDM in high-risk patients.

Cardiotoxicity

Cardiotoxicity is a very rare complication of ICIs. The reported prevalence of cardiotoxicity in patients treated with ICIs varies widely, with some reports suggesting up to 1% of patients getting affected, while others have argued that the total risk of cardiac events in

patients with ICI therapy is much higher, ranging from 3.1% to 9.7% (D'Souza et al., 2021; Rubio-Infante et al., 2021). This discrepancy may be due to misclassification and difficult diagnosis of cardiac events caused by ICIs, especially during the current COVID-19 pandemic (Totzeck, Lutgens, & Neilan, 2021). In addition, these numbers may be higher in patients taking a combination of ICIs (Johnson et al., 2016).

The most common presentation of cardiotoxicity due to ICIs is myocarditis. Patients can have a wide range of signs and symptoms, from asymptomatic to severe chest pain, dyspnea, multiorgan failure, and sudden death (Zhou et al., 2019). These symptoms usually begin within the first 3 months of immunotherapy initiation, but sometimes can begin up to a year after therapy finishes. That depends on the treatment the patient is undergoing, the patient's cancer and the type of cardiotoxicity (Zhou et al., 2019).

The mechanism of cardiotoxicity is still under investigation, but it may primarily involve CD4+ mediated T cell inflammation (Baik et al., 2021). A study by Tay *et al.* confirmed that nivolumab increases pro-inflammatory cytokine production (including tumor necrosis factor α (TNF-α), granzyme B, and interferon-gamma (IFN-γ)) in CD4+ T cells (Tay et al., 2020). ICI treatment also increased expression of the inflammatory transcription factors NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3), myeloid differentiation primary response 88 (MyD88), and p65/NF-κB in cardiomyocytes (Quagliariello et al., 2020). Substantiating this point, another study showed that anti-PD-1-treated mice had more CD4+ and CD8+ T cell infiltration in the heart as compared to a control group (Tay et al., 2020).

A study by Wang *et al.* shows that fatal myocarditis developed in mice genetically predisposed to systemic autoimmunity due to PD-1 deficiency (Wang et al., 2010). In these mice, the myocarditis was caused by CD4+ and CD8+ T cells, as well as autoantibodies against cardiomyocytes. Mice with a genetic predisposition to autoimmunity but without a PD-1 deficiency did not develop myocarditis, thus prevention of myocarditis is likely mediated by PD-1 (Wang et al., 2010). In a similar study, Love *et al.* found that CTLA-4 removal on T cells caused severe myocarditis in mice, but IL-12 deficiency prevented CD8+ T cells from proliferating, hence ameliorating the myocarditis (Love et al., 2007). Autoantibodies have also been postulated to lead to cardiotoxicity in patients treated with ICIs. A few patient cases have been reported where autoantibody deposition in cardiac muscle has been observed, suggesting a direct relationship between the antibodies and myocarditis (Martinez-Calle et al., 2018; Xu, Sharma, Tuttle, & Pokharel, 2021). However, many more cases have stated that no autoantibodies were found in histology or blood tests (Dasanu, Jen, & Skulski, 2017; Johnson et al., 2016; Michel, Rassaf, & Totzeck, 2019), leading to the conclusion that autoantibodies are generally not involved in the pathogenesis of cardiotoxicity with ICIs. Thus, the causative association of autoantibodies in cardiotoxicity needs to be further evaluated.

Atherosclerosis

Ischemic heart disease is accompanied by chronic inflammation, which substantially accelerates plaque rupture, eventually leading to myocardial infarction and stroke. When using ICIs, there are at least 2 mechanisms that have been postulated as being involved in the acute myocardial infarction: i) the activation of inflammation in preexisting plaques which triggers fibrous cap rupture and therefore acute coronary thrombosis, and ii) the direct activation of T cell-mediated coronary vasculitis in the absence of atherosclerosis. The exact mechanism associated with atherosclerosis development is difficult to be fully establish as patients with cancer may often present with concomitant cardiovascular disease. Several questions regarding the association of atherosclerosis and ICIs remain, such as whether immunotherapy increases long-term cardiovascular inflammation, possibly by transiently increasing plaque inflammatory activity. Further research is also required to determine whether acute inflammatory reactions to tumors trigger other events such as activation of platelets and

coagulation cascade, which in turn contribute to cardiovascular toxic events (Mocan-Hognogi et al., 2021).

Kidney Injury

Renal toxicities are not the most frequent toxicities associated with ICIs: the incidence of kidney injury has been reported to be 2% for ipilimumab, 1.9% for nivolumab, 1.4% for pembrolizumab, and 4.9% for the combination of ipilimumab and nivolumab (Perazella & Shirali, 2020; Wanchoo et al., 2017). An analysis of the VigiBase Pharmacovigilance database showed that the proportion of renal adverse reactions (classified by the System Organ Class "Renal and Urinary Disorders") ranged from 2.6 to 7.9%.

Contrary to conventional chemotherapies, ICIs can lead to renal injury via various mechanisms (Rosner, Jhaveri, McMahon, & Perazella, 2021). ICIs are not excreted by glomerular filtration, and display the same pharmacokinetic properties as other therapeutic antibodies, i.e. proteolytic catabolism (Centanni et al., 2019). Renal complications are mediated by immune responses with individual determinants. A recent review suggested several hypotheses to explain ICI-related renal toxicities, including the implication of gut microbiome and immunosenescence pathways (Franzin et al., 2020). ICIs could lead to the production of autoantibodies against self-antigens that share epitopes with the tumors. This has been described as a lupus-like nephropathy that occurs after ipilimumab administration (Fadel, El Karoui, & Knebelmann, 2009). Alternately, ICIs could activate self-reactive T cell clones, a phenomenon described in a case report of a patient presenting with fulminant myocarditis in which the selective clonal T cell populations infiltrating the myocardium were identical to those in tumors (Johnson et al., 2016). In the kidneys, renal tubular cells express PDL1, which protects them from T cell-mediated autoimmunity (Ding, Wu, & Gao, 2005). Furthermore, PD-L1 is frequently expressed in various renal pathologies unrelated to ICI therapy. Therefore, one possible explanation for ICI-mediated kidney injury could be antigenic overlap between normal tubular cells and tumor cells (Patel et al., 2020). Finally, ICIs could also lead to the reactivation of drug-specific T cells which could mediate kidney injury (Koda et al., 2018).

In a multicentric study of 138 patients with ICI-associated acute kidney injury, acute tubulointerstitial nephritis (ATIN) was the dominant finding in 93% of 60 biopsied patients. In addition, 45 cases of biopsy-confirmed ICI-associated glomerular disease were identified. Several other lesion types were observed, including pauci-immune glomerulonephritis (GN) and renal vasculitis (27%), podocytopathies (24%) and complement 3 glomerulonephritis (C3GN; 11%) (Mulroy et al., 2021). Thus with a wide variety of clinical manifestations and possible pathologies, addition studies are required to evaluate the renal implications of ICI therapies (Belliere et al., 2021).

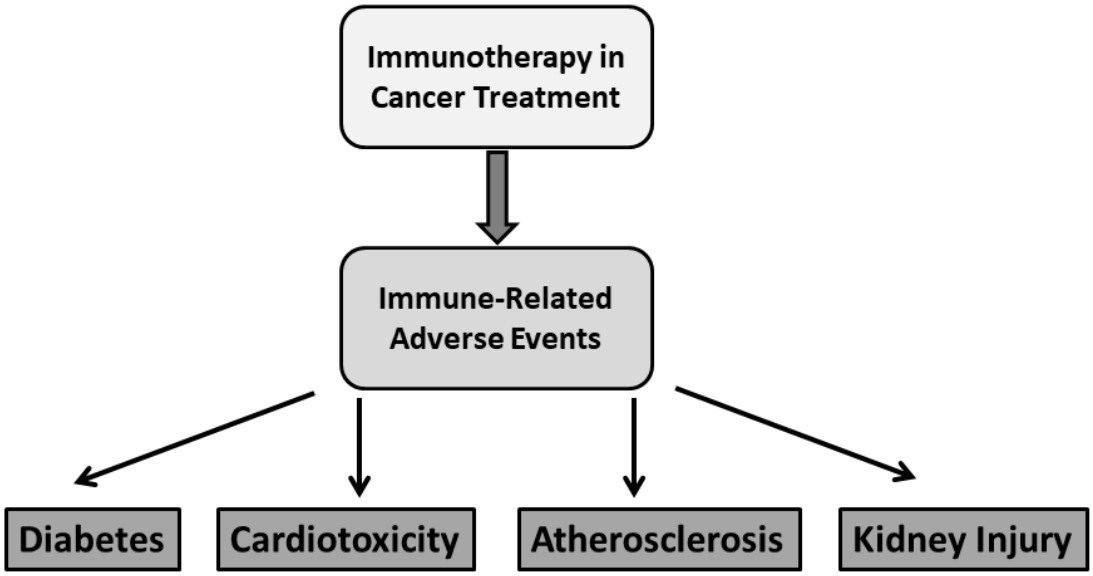

Figure 2. Immune-related adverse events associated with immunotherapies: diabetes, cardiotoxicity, atherosclerosis, and kidney injury

Immunotherapy Options and Future Promise

For many years, conventional cancer treatment has been surgery, radiotherapy, and chemotherapy (Cannon, Block, Morehead, & Knutson, 2019; Yamaguchi, 2016). While these have helped to reduce the development of cancer, incidences of relapses are a common occurrence amongst patients with malignant cancers. Immunotherapy has become a preferred solution for treating cancer because it provides different strategies against malignancies (Yamaguchi, 2016). In particular, the effectiveness of immunotherapy is that it leverages the immune system to trigger anti-tumor responses. As a result, cancer immunotherapy has gained tremendous importance in cancer therapy, courtesy of CAR T cells, cancer vaccines, and ICIs These developments have allowed oncologists to understand the relationship between adaptive and innate immune systems in mediating anticancer responses (Herrmann & Warren, 2014). However, immunotherapies are accompanied by their own unique set of adverse reactions, which pose a new challenge to practicing oncologists. Additional studies are required to reveal underlying mechanisms and possible correlations between irAEs and immunotherapy efficacy (Zhou et al., 2020).

Novel developments focus on next-generation antigen sequencing opening the door to an advanced immunotherapy era. Often, oncologists use passive immunotherapy options like mABs and lymphocytes to enhance the body's anti-tumor responses (Pietrobon et al., 2021). Active immunotherapy approaches, such as administering cancer vaccines and targeting particular antigen receptors, stimulate the host immune mechanisms. Importantly, monoclonal antibodies play a significant role in the deregulation of signal transduction pathways that facilitate tumor immune evasion (Scott et al., 2012). Thus, the FDA has approved various mABs used for the treatment of hematological malignancies. Importantly, in utilizing gene therapy and monoclonal antibody technologies, researchers have acquired significant knowledge on antigen recognition and T-cell activation, which have led to the successful development of CAR Tcells and checkpoint blockade therapy (Yee et al., 2002).

The future of cancer immunotherapy is bright because scientists can use existing knowledge to derive insights about the molecular machinery (Esfahani et al., 2020). Hence, they can conduct further trials to profile genes and determine alternative gene splicing. Currently, researchers have made significant milestones towards chromosomal

rearrangements, insertions, amplifications, and deletions in the entire transcriptome and genome. With the advent of next-generation sequencing and bioinformatic algorithms, it is possible to predict the immunogenicity of mutated genes. Future trials on tumor heterogeneity will leverage the analysis of circulating tumor DNA and advance the implementation of biomarker-based clinical trials (Yuan, 2016). Another area of focus is combinational immunotherapy, which allows different checkpoint inhibitors like anti-PD-1 to improve their efficacy. In this case, the current challenge is identifying the most effective dosage and how to formulate efficacious combinations (Zhang & Chen, 2018). With such development, the future of immunotherapeutic approaches should focus on combining different therapies yielding a robust synergistic effect.

Conclusion

The discovery of immunotherapy offers hope for cancer patients by providing an effective therapeutic option. Immunotherapy leverages natural immunity of the patient by amplifying the immune response towards invasive cancer cells, thus facilitating tumor lysis and regression. In other instances, immunotherapy vaccines strengthen the innate immune system to enhance their efficacy in fighting tumors. Despite the progressive development in cancer diagnosis, treatment, and management using immunotherapy, more work remains to be done. However, the future of cancer treatment using immunotherapy is encouraging.

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Abbreviations

Immune-Related Adverse Effects (irAEs)
International Agency for Research on Cancer (IARC)
Natural Killer (NK) cells
Class II Major Histocompatibility Complex (MHC-II)
Food and Drug Administration (FDA)
Interleukin-2 (IL-2)
Monoclonal Antibodies (mABs)
Antibody Dependent Cell-Mediated Cytotoxicity (ADCC)
Epithelial Cell Adhesion Molecules (EPCAM)
Interferon-α (IFN-α)
Natural Killer (NK)
Tumor-Infiltrating Lymphocytes (TILs)
T Cell Receptors (TCRs)
Chimeric Antigen Receptor T cells (CAR T cells)
Bacillus Calmette-Guerin (BCG)
Toll-Like Receptors (TLRs)
Immune Checkpoint Inhibitors (ICIs)

Overall Response Rate (ORR)
Progression-Free Survival (PFS)
Overall Survival (OS)
Ici-Induced Diabetes Mellitus (Icidm)
Type 2 Diabetes Mellitus (T2DM)
Non-Obese Diabetic (NOD)
Cytotoxic T-Lymphocyte-Associated Protein 4 (CTLA-4)
Programmed Cell Death (PD-1)
Programmed Cell Death Ligand 1 (PD-L1)
Forkhead Box Protein P3 (FoxP3)
Regulatory T Cells (Treg) cells
Tumor Necrosis Factor α (TNF-α)
Interferon-Gamma (IFN-γ)
NOD-, LRR- and Pyrin Domain-Containing Protein 3 (NLRP3)
Myeloid Differentiation Primary Response 88 (MyD88)
Tubulointerstitial Nephritis (ATIN)
Glomerulonephritis (GN)
Complement 3 Glomerulonephritis (C3GN)

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