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Cancer immunotherapy and cardiovascular side-effects: from treatment modalities to the use of the preventive effect of antihypertensive drugs

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Abstract

Cancer treatment regimens are significantly more intricate than commonly perceived. Nonetheless, both immunotherapy and chemotherapy may produce adverse consequences. Immunotherapy represents a significant advancement in the battle against cancer; nonetheless, it is not devoid of challenges. This research elucidates the mechanisms underlying immunotherapy-induced cardiovascular damage, highlighting the significant role of immune regulators, such as soluble urokinase plasminogen activator receptor (suPAR), in inducing vascular leakage. We also examine the role of matrix metalloproteinase (MMP14/15) in this process, and antigens associated with cardiovascular illness and malignancies, including native proteins, mutated tumor antigens, and viral components. Besides, we studied predictive biomarkers, such as circulating T-cell populations associated with the probability of myocarditis. We discuss treatment approaches and strategies to mitigate these issues, particularly through the use of antihypertensive medications to reduce their impact. Losartan alters the tumor microenvironment (TME) to improve immunotherapy. It restores immune effector cells in triple-negative breast cancer (TNBC), overcomes resistance in unresponsive tumors, and modifies TMEs' immune system suppression in ovarian cancer and melanoma. It is important to note that its effects differ by cancer kind. It may promote fibrosarcoma tumor growth and improve cholangiocarcinoma treatment. This shows that losartan's dangers in cancer treatment should be carefully considered and that more research is needed. This suggests

that there must be careful consideration of the potential risks associated with losartan use in cancer treatment and underscores the requirement for additional research on this topic. This study may enhance our comprehension and management of cardiovascular adverse effects in cancer immunotherapy by integrating novel insights on immunological predictors and vascular dysfunction. Experts assert that oncology programs must provide and promote continuous monitoring of cardiac health for breast cancer patients. To mitigate the risk of cardiovascular disease in this demographic, comprehensive patient care must be administered.

Keywords

cardiovascular diseases (CVD), immune checkpoint inhibitors (ICIs), immunotherapy, cancer, side-effects

Introduction

Immunotherapy is a sort of biological therapy that uses parts of living things to fight cancer. In immunotherapy, drugs are given to the patient to make their immune system stronger. As the body's immune system gets stronger, people become better at fighting off cancer cells, which eventually leads to the death of cancer cells. Immunotherapy drugs do not directly assault tumors. Instead, they make it easier for the immune system to find and eliminate them by strengthening it. Immunotherapy is a new way to treat cancer that makes the immune system better at finding and fighting cancer cells. Scientists have worked on different immunotherapy methods to treat some types and stages of cancer over the past ten years [1]. Immunotherapy drugs help cure cancer by boosting the body's immune response. These drugs work in different ways. Some medications may help the immune system recognize and fight cancer.

However, in many cases, immunotherapy makes the immune system stronger. At certain times, each type of immunotherapy is tested and approved for use on certain types of cancer. These treatment plans are only approved for certain types and stages of cancer. Researchers continually explore new combinations of treatments to utilize this method in treating various forms of cancer, although it is not always employed. Immunotherapy can be used on its own or alongside other treatments such as chemotherapy, radiation therapy, surgery, and other drugs [2]. FDA-approved immunotherapy drugs are used to treat some types of tumors, usually in the later stages of the disease when surgery is not an option [3]. In some instances, they can either extend a person's life or slow down the growth of cancer. Immunotherapies have recently been used as a first-line treatment for early-stage cancers. Sometimes, when immunotherapies work, people may not need other treatments, like chemotherapy.

Treating cancer is more complex than it may appear; both immunotherapy and chemotherapy can produce adverse consequences. No singular cancer treatment is superior to all others. Immunotherapy frequently presents side effects that are either more or less controllable. Nonetheless, specific individuals may experience severe adverse effects from the injections or develop immunological reactions that compel them to discontinue the medication. This is further exacerbated by the difficulty in comparing the efficacy of immunotherapy with that of chemotherapy. Both therapeutic approaches utilize various pharmacological agents and apply to distinct cancer kinds and stages. Radiation therapy remains consistent. Certain malignancies require just radiation therapy, whilst others exhibit improved responsiveness to a combination of chemotherapy and radiation. These may pertain to the individual's immune system genes or the genes associated with the cancer. Immunotherapy agents enhance the immune system's ability to identify and combat cancer cells more efficiently. Various forms of immunotherapy are employed in cancer treatment, each functioning through distinct mechanisms.

Immune checkpoint inhibitors (ICIs) prevent the body's natural defense from inhibiting immune cells from targeting healthy cells. Specific cancer cells exploit these checkpoints to evade detection by the immune system. In this manner, inhibitors can assist the immune system in locating and combating cancer cells. ICIs may induce adverse effects, including dermatological responses, gastrointestinal disturbances such as nausea and diarrhea, as well as exhaustion or pyrexia. Graver adverse effects encompass infusion

reactions, autoimmune responses, and extensive inflammation. Cancer vaccines are a form of immunotherapy that enhances the immune system's ability to combat cancer. Numerous vaccines enhance individuals' immune systems, thereby preventing illness caused by viruses and bacteria. Certain vaccines are prophylactic, indicating their role in combating oncogenic viruses. Certain vaccinations are therapeutic and assist the immune system in combating cancer. The majority of vaccines administered for disease prevention have few side effects. Cancer treatment vaccines may induce flu-like symptoms. Specific components of the vaccination may elicit severe allergic responses. Cancer treatment vaccines carry several dangers, including stroke, tumor lysis syndrome, and herpes virus infection. This procedure extracts immune cells from the cancer patient's body. Cells are altered in the laboratory to improve their capacity to combat cancer, subsequently being reintroduced into the patient. This therapy employs a specific virus to facilitate the adhesion of T cells, a kind of immune cell, to tumor cells for their destruction. Cell therapy may result in a condition known as capillary leak syndrome. This approach demonstrates that proteins and fluids can translocate from blood vessels into adjacent tissues. This issue reduces blood pressure, potentially leading to organ failure and shock. Typically, these drugs enhance the immune system and may assist in combating some types of cancer.

Hereditary or congenital heart diseases (CHD) are among those CVDs that cause multiple problems for sufferers from birth [4]. Among the most important types of this group of heart diseases are defects in the wall between the ventricles and congenital defects in the heart atria, and these diseases require rapid control and intervention [5]. Cardiac arrhythmias are problems associated with disturbances in the heartbeat and rhythm, and the main reason for this phenomenon is the presence of various disorders, which is in the path of the heart's electrical currents [6]. Among the most important examples of these diseases are tachycardia and bradycardia. Cardiomyopathy diseases affect the heart muscles, reducing blood pumping to the body's tissues and causing numerous problems for sufferers [7]. CVD has become more prevalent in recent years, and the reason for this is the change in people's lifestyles [8].

Cytokines function as immunological modulators. These little proteins transmit signals between cells and instruct immune cells to target cancer cells. Certain immune-modulating medications may induce flu-like symptoms, including fever, chills, weakness, disorientation, nausea, vomiting, musculoskeletal pain, fatigue, and headaches. Cytokines may induce significant adverse effects, including respiratory complications, fluctuations in blood pressure (both hypotension and hypertension), allergic reactions, decreased blood cell counts increasing susceptibility to infections and hemorrhaging, thrombosis, alterations in mood, behavior, cognition, and memory, as well as dermatological manifestations such as rashes, burning sensations, or lesions, and organ damage. Targeted therapy is a form of cancer immunotherapy that employs monoclonal antibodies. The immune system produces antibodies, which are proteins. They are intended to identify proteins associated with cancer or tumors [9].

Various symptoms such as chronic or sudden chest pain, shortness of breath, nausea, chronic fatigue, severe weakness, fainting, feeling cold in the fingertips and toes, feeling pain in the neck and lower jaw, palpitations, excessive sweating, and chest pain during exercise are among the most common symptoms. However, these symptoms can also occur in other diseases and the presence of these diseases cannot be detected by observing these clinical symptoms alone, and it is necessary to use various clinical tests and medical techniques to better diagnose these diseases [10]. The various types of immunotherapy drugs lead to differing costs. Cancer immunotherapy may occasionally surpass $100,000 per person. Nonetheless, numerous orally taken pharmaceuticals are relatively straightforward to produce and may be significantly more economical. Personalized cell therapies, which require the manipulation and development of cells in a laboratory, may entail expenses totaling hundreds of thousands of dollars. Immunotherapy constitutes a novel strategy for cancer treatment. It utilizes the immune system to fight cancer. FDA-approved immunotherapies target many malignancies, including brain, colorectal, skin, and lung tumors, among others [11]. The characteristics and stage of the malignancy will determine the suitability of immunotherapy. Immunotherapy may be provided alone or in combination with other oncological treatments. Immunotherapy is an innovative and promising method for cancer treatment; yet, it is still in the developmental stage. It is not uniformly efficacious for all cancer patients and does not ensure success in every instance.

Cancer immunotherapy

The immune system consistently identifies and eliminates aberrant cells, likely preventing the proliferation of numerous malignancies. Occasionally, immune cells are observed within and around malignancies. Tumor-infiltrating lymphocytes (TILs) demonstrate the immune system's response to cancer [12]. Individuals with malignancies exhibiting TILs demonstrate superior outcomes compared to those whose tumors lack TILs. The immune system can inhibit the proliferation or metastasis of cancer; yet, cancer cells possess mechanisms to evade destruction by the immune system. Immunotherapy is a treatment modality that utilizes pharmacological agents to enhance an individual's immune system, enabling it to identify and eradicate cancer cells. This therapy is occasionally employed in the treatment of bladder cancer [13]. Intravesical Bacillus Calmette-Guerin (BCG) is a combination of the pathogens responsible for tuberculosis. It does not consistently induce illness, although it may elicit an immunological response [14]. BCG can be administered to the bladder in liquid form, prompting immune cells within the bladder to combat cancer cells. One of the primary functions of the immune system is to safeguard the body's normal cells from assault. Checkpoint proteins are present in immune cells and must be activated or deactivated for an immune response to occur. Programmed cell death protein 1 (PD-1) and programmed cell death ligand 1 (PD-L1) inhibitors target a protein on the cell surface that inhibits the immune system's ability to combat cancer cells [15]. These pharmaceuticals inhibit PD-L1, hence enhancing the immune system's capacity to combat cancer cells. This may result in reduced tumor size or diminished growth rate. Nivolumab and pembrolizumab are agents that inhibit the PD-1 protein on the surface of specific immune cells (T-cells), preventing them from engaging in self-attack. Blocking PD-1 enables the immune system to target cancer cells, resulting in tumor reduction and deceleration of growth [16].

Cancer cells can alter their DNA to evade detection by the immune system, express surface proteins that inhibit immune cell function, or modify adjacent normal cells, complicating the immune response to cancer cells [17]. Various forms of immunotherapy are employed in cancer treatment. Immunomodulatory inhibitors are pharmacological agents that inhibit immunological regulators, hence altering the immune system and mitigating an excessive immune response [18]. Inhibiting these regulators enhances the malignancy's susceptibility to the pharmaceuticals. T-cell transfer is a therapeutic approach for cancer that enhances the efficacy of T-cells in combating the disease. This therapy extracts immune cells from the tumor. In the laboratory, anti-cancer chemicals are isolated or modified to enhance their efficacy against cancer cells, and subsequently administered intravenously using a syringe. Monoclonal antibodies are laboratory-produced proteins specifically engineered to attach to cancer cells exclusively. Targeted monoclonal antibodies identify cancer cells, enhancing their visibility and increasing the likelihood of their destruction by the immune system [19]. Therapeutic vaccines enhance the immune system's capacity to combat malignant cells. These immunizations differ from those that prevent illness. Immune modulators enhance the immune system's efficacy in combating cancer. Some medications target specific components of the immune system, whilst others affect the immune system in its entirety. Numerous cancers can be addressed with immunotherapy agents; nevertheless, immunotherapy is less efficacious than surgery, chemotherapy, or radiation therapy [20].

Immunotherapy is typically administered via intravenous infusion, oral tablets or capsules, topical creams for early-stage skin cancer, or directly into the bladder. Immunotherapy can be administered at a clinic or as outpatient surgery in a hospital setting [21]. Despite outpatient status indicating that hospitalization is unnecessary, clinicians assert that immunotherapy should be conducted exclusively in adequately equipped cancer treatment facilities [22]. The type and stage of cancer, together with the body's response to treatment, influence the frequency and duration of immunotherapy administration. Specific forms of immunotherapy are administered in cycles. Each cycle comprises a treatment phase and a recovery phase. Cancer can recuperate, react to treatment, and generate new healthy cells during periods of remission. A comprehensive physical examination, along with blood tests and further imaging examinations, will be conducted to evaluate the efficacy of immunotherapy. These tests will reveal the tumor's dimensions and any alterations in blood markers [23].

Researchers are concentrating on critical domains to enhance immunotherapy, particularly in addressing drug resistance. Researchers are investigating the efficacy of combining immunomodulatory inhibitors with various forms of immunotherapy, targeted therapy, and radiation for patients who do not respond to immunotherapy [24]. They are also seeking methods to anticipate individuals' responses to immunotherapy. A limited cohort of individuals undergoing immunotherapy exhibits a favorable response to the treatment. Consequently, a significant study focus is determining whether patients may derive benefit from it [25]. This entails acquiring further knowledge of the mechanisms by which the immune system targets or inhibits them. A more profound comprehension of how cancer cells evade the immune system could assist scientists in developing novel pharmaceuticals that specifically target this mechanism. Researchers are diligently striving to mitigate the adverse effects of immunotherapy [26].

The effects of cancer treatment on cardiovascular health

At times, cancer therapy appears illogical. Radiation therapy and chemotherapy have transformed cancer treatment; yet, they may potentially adversely affect cardiac health [27]. Understanding the impact of these drugs on cardiac function is crucial. Radiation therapy may induce myocardial infarctions, cardiac insufficiency, and arrhythmias. Chemotherapy, whether traditional or contemporary, can adversely affect the heart and vascular system. This may result in complications related to coagulation or lipid metabolism. Certain side effects manifest immediately during chemotherapy, but others may not become apparent until years' post-treatment.

The adverse effects of chemotherapy on the cardiovascular system are typically associated with the cumulative dosage of chemotherapeutic agents administered or the concurrent administration of various medications types. Radiation therapy administered to various body regions before a stem cell transplant may induce cardiac complications [28]. This is contingent upon the quantity of radiation administered to the chest and the extent of heart tissue within the treatment zone. Chemotherapy, stem cell therapy, and radiation therapy can damage the heart and induce arrhythmias [29]. Cardiac conditions may encompass cardiomyopathy, congestive heart failure, valvular damage resulting in stenosis or regurgitation, coronary artery disease, pericarditis, pericardial fibrosis, pericardial effusion, and carotid artery disease. The manifestations of cardiovascular illness might vary significantly based on the specific condition. In these circumstances, only diagnostic assessments can identify the issue. Before initiating cancer treatment, assessments are conducted before, during, and after the treatment to evaluate alterations in the heart's structure and function [30]. Assessments conducted during cancer treatment are crucial for mitigating complications associated with the cardiovascular system. Should the oncologist perceive a potential for cardiovascular-related adverse effects, they will either reduce the dosage of chemotherapy or radiotherapy or discontinue treatment entirely to prevent additional injury.

The association between cancer immunotherapy and cardiovascular inflammation

Immunotherapy for cancer has transformed the treatment of numerous cancers. However, in a small percentage of patients, this life-saving medication may induce myocarditis, a severe inflammation of the heart muscle [31]. Halting and remedying this potentially lethal condition is challenging due to our lack of understanding regarding its etiology and mechanisms. A recent study revealed that immune cells and connective tissue cells within cardiac muscle initiate the immunological response responsible for inflammation [32]. Research has identified distinct blood anomalies that may indicate an increased mortality risk in myocarditis patients [33]. Research indicates that the immune response in the heart and blood arteries differs from that directed against malignancies [34]. This suggests that personalized therapies can help patients continue to receive the necessary cancer immunotherapy. A recent trial is testing an anti-inflammatory medication as a potential method to mitigate heart inflammation induced by immunotherapy. This discovery provides scientists with a scientific rationale to develop more personalized therapies for myocarditis induced by ICIs [35].

The relationship between immunotherapy and cardiovascular issues is intricate and largely contingent upon the specific treatment employed [36]. The degree of variance is contingent upon the specific immunotherapy formulation, as distinct types of immunotherapy, such as checkpoint inhibitors and immune cell therapies, exhibit diverse effects. ICIs, including anti-PD-1/PD-L1 and anti-CTLA-4 agents, may induce myocarditis by directing T lymphocytes against cardiac antigens, resulting in cardiac inflammation. The immune system's capacity to both combat disease and damage cardiac tissues is a compelling aspect of immunotherapy. Conversely, adoptive cell therapies, particularly CAR-T cell treatments, have a higher propensity to induce cytokine release syndrome (CRS). This adverse consequence may induce systemic endothelial dysfunction and hemodynamic instability, hence increasing the strain on the heart's functionality.

Cytokine-based immunotherapies such as IL-2 and IFN-α may elevate the risk of hypertension and arrhythmias due to their propensity to induce vascular inflammation and fluid retention. The fundamental mechanisms, including autoreactive T-cell infiltration (seen with ICIs), cytokine storms (linked to CAR-T therapies), or unintended vascular effects from cytokine treatments, significantly influence both the symptoms and their management. Therefore, it is incumbent upon healthcare providers to thoroughly understand these formulation-specific pathways. This information is essential for accurate risk assessment, prompt diagnosis, and the implementation of tailored cardioprotective strategies. This approach will assist physicians in addressing the challenges of immunotherapy while safeguarding cardiac health should new therapeutic options emerge.

Myocarditis is an uncommon yet severe adverse effect that impacts around one-third of cancer patients in the United States whose tumors may respond favorably to ICIs, which are pharmacological agents that enhance the immune system's ability to combat cancer. The increasing number of individuals receiving ICIs annually is elevating the probability of severe problems and the intricacy of managing them. Even after discontinuing treatment, it may be challenging to halt or reverse these effects, and patients may experience organ inflammation that might be fatal with a single dose of the medicine. A minimal proportion of individuals receiving ICIs develop myocarditis. This number increases among those receiving a combination of specific immunotherapy agents. Myocarditis associated with ICIs can result in significant cardiac complications, including arrhythmias and heart failure, in 50% of instances [37]. Approximately one in three individuals afflicted with this kind of myocarditis succumb, despite optimal therapeutic interventions. Alternative forms of myocarditis, particularly those induced by viral infections, exhibit resistance to therapeutic interventions and supportive care [38].

The recent discoveries are based on the analysis of blood, cardiac, and tumor tissue samples from individuals who developed myocarditis following the administration of immune checkpoint inhibitor therapy [39]. Cardiac tissue possesses a greater number of molecular mechanisms that facilitate the recruitment and retention of immune cells associated with inflammation. Individuals exhibiting illness demonstrated an increased presence of cytotoxic T-cells, dendritic cells, and inflammatory fibroblasts. The researchers observed a reduction in immune cells in the blood, including plasmacytoid dendritic cells, dendritic cells, and B cells, which are crucial for combating infections [39]. Conversely, there was an increase in mononuclear macrophages, a category of immune cells. The scientists examined T-cell receptors, a category of proteins that react to foreign entities known as antigens. The T-cell receptors in the injured cardiac tissue differed from those present in the tumors. No evidence existed to demonstrate that the T-cell receptors identified the cardiac muscle protein alpha-myosin, previously established as a significant antigen in the pathogenesis of immunotherapy-induced myocarditis. The data suggest that T-cell receptors prevalent in sick cardiac tissue can identify previously unrecognized antigens.

Antihypertensive medications may mitigate immunotherapy-induced cerebral edema

Immunotherapy agents have demonstrated the ability to stimulate the immune system to target cancer cells. Patients reportedly develop cerebral edema during treatment [40]. Steroid therapy is employed to

manage cerebral edema. These steroids exert immunosuppressive effects that diminish the efficacy of immunotherapy agents [41]. Consequently, there is a need for novel pharmaceuticals that can address edema without compromising immune function. Recent studies indicate that losartan can modify the TME to enhance the efficacy of immunotherapy. It aids in the restoration of immune effector cells in triple-negative breast cancer (TNBC), circumvents resistance in tumors unresponsive to treatment, and alters the mechanisms by which TMEs suppress the immune system in ovarian cancer and melanoma. However, it is crucial to acknowledge that its effects may vary among different cancer types. For instance, it may facilitate tumor proliferation in fibrosarcoma while exhibiting enhanced efficacy with treatment in cholangiocarcinoma. This indicates the necessity for cautious consideration and additional investigation about the potential risks associated with the use of losartan in cancer treatment.

Research indicates that losartan, an antihypertensive medication, effectively mitigates cerebral edema induced by immunotherapy. The concurrent administration of immunotherapy medicines and losartan does not result in adverse effects [42]. Research utilizing murine cancer models, genetic sequencing of neoplastic cells, neuroimaging of patients, and investigations into the inhibition of immune cell activity have demonstrated that immunotherapy induces edema in individuals with brain tumors due to an inflammatory response impacting the blood-brain barrier. Matrix metalloproteinase 14 and 15 (MMP14 and MMP15), located in the cells of the tumor vasculature's inner wall, induce vascular leakage during this inflammatory response, resulting in edema [43]. Research indicates that the antihypertensive medication diminishes edema induced by anticancer immunotherapy by inhibiting the production of certain enzymes. Losartan enhances the immunological response of the body against malignancies (Table 1). Research indicates that administering losartan in conjunction with other immunotherapeutic agents enhances survival rates in mice afflicted with glioblastoma [44, 45].

Table 1. Studies on the use of losartan in patient with cancer exposed to immunotherapy.

Study ID, reference	Target model	Participant details	Immunotherapy technique	Cancers	Mechanism	Findings
Yang et al., 2025, [46]	Acidic TME	Post-exposure effect	ICIs-CT	TNBC	Losartan in the acidic TME	Significant restoration of IEC and lower TV
Hou et al., 2024, [47]	84 patients	Post-combination therapy side effects	PD1/PD-L1-CT	Ref-Tum	Losartan in the TMME	Overcome immunotherapy resistance
Sun et al., 2024, [48]	TME	Post-exposure effect	ICIs-CT	OvCa	Losartan in the TME	Reprogramming the TME
da Silva et al, 2024, [49]	TME	Post-exposure effect	TRAIL	ColCa	Losartan in the TME	Inhibit tumor progression
Sun et al., 2024, [50]	Mice (5–6 weeks, 19–20 g)	Post-exposure effect	PD1-CT	FibSarc	Losartan on PD1ab	Promoted cancer growth
Liu et al., 2024, [51]	TME	Post-exposure effect	PD1-CT	----	Losartan in TIME	Remodeling the TIME
Ramzy et al., 2024, [52]	Mice (8–10 weeks, 20–25 g)	Post-exposure effect	PD1-CT	Mel	Losartan in the TME	Reprogramming the TME
Puopolo et al., 2023, [53]	TME	Post-exposure effect	PD1/PD-L1-CT	----	Losartan in the TME	Block the PD-1/PD-L1 interaction
Li et al., 2023, [54]	Mice randomized into four groups (n = 7 mice/group)	Post-combination therapy side effects	ICIs-CT	BrsCa	Losartan in the TME	Inhibit α-SMA
Li et al., 2023, [55]	TME	Post-exposure effect	DP	SolTu	Losartan in the TME	Remodeling the TME
Ammons et al., 2022, [56]	10 dogs	Post-combination therapy side effects	TME-MI	Glio	Losartan in the TME	Remodeling the TME

Table 1. Studies on the use of losartan in patient with cancer exposed to immunotherapy. (*continued*)

Study ID, reference	Target model	Participant details	Immunotherapy technique	Cancers	Mechanism	Findings
Li et al., 2022, [57]	170 patients	Post-combination therapy side effects	PD1/PD-L1-CT	CCA	Oral Losartan	Enhance the effectiveness of adjuvant chemotherapy
Zhao et al., 2022, [58]	Mice (6–8 weeks old, female)	Post-combination therapy side effects	PD1/PD-L1-CT	TNBC	Losartan plus CT	Improve CT
Regan et al., 2019, [59]	Mice (5–6 weeks, 19–20 g)	Post-combination therapy side effects	Mono-machro	LungCa	Losartan in the TME	Suppress lung metastasis

TNBC: triple-negative breast cancer; TME: tumor microenvironment; IEC: immune effector cells; TV: tumor volume; ICIs: immune checkpoint inhibitors; CT: combination therapy; Ref-Tum: refractory tumors; TMM: tumor mechanical microenvironment; OvCa: Ovarian cancer; TRAIL: tumor necrosis factor-related apoptosis-inducing ligand; ColCa: Colon cancer; FibSarc: fibrosarcoma; PD1ab: programmed cell death protein 1 antibody; TIME: tumor immunosuppressive microenvironment; Mel: melanoma; BrsCa: breast cancer; α-SMA: alpha-smooth muscle actin; SolTu, DP, solid tumors: dendritic macromolecule loaded with doxorubicin (PAMAM-ss-DOX); Glio: glioma; TME-MI: TME modifying immunotherapy; CCA: cholangiocarcinoma; LungCa: lung cancer; Mono-machro: monocyte and macrophage.

Losartan is an angiotensin receptor antagonist that has demonstrated encouraging albeit context-dependent outcomes when administered alongside immunotherapy for various cancer types. Losartan was found to reinstate the functionality of immunological effector cells (IECs) and reduce tumors in individuals with TNBC [46]. In ovarian cancer and melanoma, it altered the TME to enhance the efficacy of immunotherapy [48, 52]. Losartan was capable of overcoming immunotherapy resistance in refractory cancers, which are malignancies unresponsive to conventional treatments [47]. It also inhibited the proliferation of colorectal cancer by altering the TME [49]. In fibrosarcoma, losartan accelerated tumor growth when administered alongside anti-PD1 therapy [50]. This underscores the significance of doing cancer-specific diagnostics.

Mechanistically, losartan's advantages often include modifying the TME, hence affecting the cellular composition and physical characteristics of the TME. This encompasses a reduction in α-SMA expression [54] and a disruption in the interactions between PD-1 and PD-L1 [53]. It enhanced the efficacy of chemotherapy in TNBC and cholangiocarcinoma [55, 58] and inhibited lung metastasis in animal models not yet evaluated in people [50]. However, its effects varied between different types of immunotherapy. For instance, it demonstrated efficacy with ICIs in TNBC and melanoma. However, its efficacy was limited in glioblastoma [56]. These results indicate that losartan can be both beneficial and detrimental, necessitating further research to determine optimal applications in conjunction with specific cancer and immunotherapy combinations.

Discussion

Immunotherapy is a game-changer for treating cancer, but it is not without its problems. One of these problems is that it can cause harmful effects on the heart, such as myocarditis, which is a serious inflammatory response in the heart muscle. This paper goes into detail on the processes behind immunotherapy-induced cardiovascular damage, focusing on the interesting involvement of immune regulators like soluble urokinase plasminogen activator receptor (suPAR) in causing vascular leakage. We also investigate the role of MMP14/15 in this process. Recent research shows that losartan can change the TME to make immunotherapy work better. It helps restore immune effector cells in TNBC, overcomes resistance in tumors that do not respond to treatment, and alters the way TMEs suppress the immune system in ovarian cancer and melanoma. However, it is important to know that its effects can be different for different types of cancer. For example, it might help tumors grow in fibrosarcoma but work better with chemotherapy in cholangiocarcinoma. This highlights the importance of carefully considering and further studying the potential hazards associated with using losartan for cancer treatment.

In this case, a systematic review and meta-analysis looked at the cardiovascular toxicity of immunotherapy in patients with non-small cell lung cancer (NSCLC) by combining data from 12

observational studies with a total of 23,621 participants. The study showed how often and what kinds of heart problems, like myocarditis, arrhythmias, and high blood pressure, are connected to ICIs. The results showed that this group of people needs more careful monitoring and management of their cardiovascular risks. There were several problems with the study, such as the fact that the studies were not all the same. However, it gave doctors useful information and suggested that more research is needed to improve risk categorization and mitigation measures [60]. A new systematic review and meta-analysis looked into cardiotoxicity caused by ICIs in lung cancer patients. The analysis combined data from 30 trials with 16,331 individuals to look at the frequency, clinical signs, and outcomes of cardiovascular problems such as myocarditis, pericarditis, and heart failure that are linked to ICIs. The results showed a significant but variable risk of cardiotoxicity, which stressed the importance of early detection and therapy by a team of experts. The authors acknowledged several limitations of the study, including its differences from other studies, but they provided valuable insights into risk factors and potential prevention methods. This study emphasizes the importance of regular heart checks for lung cancer patients undergoing immunotherapy. This makes our audience feel accountable and proactive in their patient care [61].

Researchers examined the cardiovascular toxicity of ICIs across different malignancies in a meta-analysis of 57 randomized clinical trials with 12,118 individuals. The study examined the frequency, types, and severity of cardiovascular side effects, including myocarditis, arrhythmias, and vasculitis, to assess their impact on patients. The results showed that ICI-related cardiotoxicity is not very common, but when it does happen, it can be pretty serious and even fatal; therefore, close monitoring is necessary. The authors noted that one limitation of the studies was their variability, yet they collectively provided valuable insights into risk management and stratification. This study contributes to the growing body of research on the cardiovascular hazards of cancer immunotherapy, emphasizing the need for multidisciplinary treatment. It highlights the importance of collaboration among different professionals in patient care [62]. A new systematic review and global meta-analysis looked at the incidence, risk factors, and clinical outcomes of cardiotoxicity linked to cancer immunotherapy in 101 RCTs with 58,698 participants. The study combined data from several groups of patients and focused on the most important cardiovascular problems that are associated with ICIs, such as myocarditis, pericardial disease, and heart failure. The results showed that the rates of cardiotoxicity varied a lot depending on the kind of cancer and the treatment plan, with some patient groups at higher risk than others. The authors stressed how important it is to find problems early, assess the risks, and manage them with a team of experts to lessen the adverse effects and provide healthcare workers with the tools they need to respond. This meta-analysis provides valuable global insights into the cardiovascular risks associated with ICI, despite certain limitations, such as the variability in study design. This information can be used to improve clinical practice and guide future research [63]. Recent research examines the key challenges arising from the intersection of cancer immunotherapy and heart health, aligning with our findings. The study looks at how ICIs can cause cardiotoxicity, what the risk factors are, and what the clinical signs are, with a focus on problems including myocarditis, arrhythmias, and vascular dysfunction. The authors stress the need for oncologists and cardiologists to work together more often to improve patient monitoring, early identification, and treatment plans. They also discuss topics we do not yet understand, such as the lack of standard procedures for assessing a patient's cardiovascular risk during immunotherapy. This review highlights the importance of further research to strike a balance between the effectiveness of cancer treatments and their safety for the heart, particularly in the context of advanced cancer treatments [64].

Limitation

This study has several limitations, including its inability to present a statistical analysis of the percentage of patients who experienced cardiovascular complications post-immunotherapy or the exact impact of antihypertensive medications. This is attributable to the research employing varied designs and failing to provide adequate data. Consequently, it was challenging to perform a thorough quantitative assessment. The key focus of future research should be the standardization of reporting cardiovascular events and antihypertensive medication responses in patients undergoing immunotherapy. This could substantially enhance meta-analyses and aid medical professionals in decision-making.

Conclusions

The researchers aim to determine whether heart and cancer antigens are native proteins, mutant tumor proteins, viruses, or other entities. Recent research indicates that blood T-cell populations can be utilized to forecast an individual's likelihood of mortality from myocarditis. This may enable the utilization of a blood test to identify those at risk who require specialized care or should be excluded from immunotherapy. The findings indicate that diagnostic blood testing may replace invasive cardiac biopsies in patients with myocarditis. Experts assert that immunotherapy treatments are remarkable and can be life-saving; so, patients should not fear them. Our objective is to enhance their efficacy to maximize cancer-fighting advantages while minimizing undesirable effects. Cardiovascular disease is the predominant cause of mortality in the United States, and therapeutic alternatives are limited. Most therapies for cardiovascular illness do not target the heart directly. They concentrate on diabetes, hypertension, nutrition, and physical activity. Statins facilitate the reduction of cholesterol levels. Recent findings indicate that an immune protein may significantly contribute to atherosclerosis, the hardening of the coronary arteries. This creates fresh avenues to tackle a problem that impacts nearly all elderly individuals. Atherosclerosis is a condition characterized by the accumulation of fatty deposits and other substances that obstruct and constrict arteries. Coronary vascular occlusions can result in myocardial infarction or angina. Numerous potential causes exist. This inquiry primarily focuses on the role of the immune system. We have identified the initial component of the immune system that meets all criteria to serve as a target for atherosclerosis therapy. The primary objective of heart disease treatment is to address immunology during atherosclerosis progression.

Research indicates that breast cancer increases the risk of heart failure, cardiomyopathy, and other cardiovascular complications. The cohort of women with breast cancer had elevated mortality rates from cardiovascular disease and overall mortality, with risk variations contingent upon the treatment administered. Women undergoing chemotherapy, radiotherapy, and aromatase inhibitors exhibit an increased likelihood of developing heart disease. Experts assert that oncology programs must provide and promote continuous monitoring of cardiac health for breast cancer patients. To mitigate the risk of cardiovascular disease in this demographic, comprehensive patient care must be administered.

Abbreviations

BCG: Bacillus Calmette-Guerin

CVD: cardiovascular diseases

ICIs: immune checkpoint inhibitors

MMP14/15: matrix metalloproteinase 14/15

PD-1: programmed cell death protein 1

PD-L1: programmed cell death ligand 1

TILs: tumor-infiltrating lymphocytes

TME: tumor microenvironment

TNBC: triple-negative breast cancer

Declarations

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Author contributions

FR: Conceptualization, Investigation, Writing—original draft, Writing—review & editing. ABQ: Conceptualization, Investigation, Writing—original draft, Writing—review & editing. SG: Conceptualization, Investigation, Writing—original draft, Writing—review & editing. IB: Conceptualization, Investigation,

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The authors declare that they have no conflicts of interest.

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