REVIEW ARTICLE

Risk Factors and Emerging Therapies for Immune Checkpoint Inhibitor-related Myocarditis: A Narrative Review

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Abstract

Background: Immune checkpoint inhibitors (ICIs) represent a groundbreaking development in immunotherapy, offering significant promise in the treatment of various malignancies previously considered incurable. However, despite their potential benefits, the increasing use of ICIs is associated with a spectrum of immune-related adverse events (irAEs). Myocarditis is a rare and potentially underestimated complication that represents the highest mortality rate among irAEs.

Objective: The review aims to evaluate the current understanding of ICI-myocarditis (ICI-M) through providing a detailed overview of diagnostic challenges, screening strategies, and, in particular, the risk factors and evolving treatment agents beyond corticosteroids.

Materials and methods: A comprehensive literature review was conducted on PubMed, analyzing data from relevant clinical studies, case reports, preclinical models, and expert consensus guidelines. In addition, data from one ongoing clinical trial (ATRIUM trial) not yet indexed in PubMed were included to reflect emerging therapeutic developments.

Results: Despite the low incidence of ICI-M (0.06%–1%), which is likely underestimated, the mortality rate is the highest among irAEs; the most identifiable risk factors include combination therapy with ICI agents (anti-PD1 and anti-CTLA-4), preexisting cardiovascular and autoimmune diseases, use of ICIs alongside other anticancer treatments, certain tumor types, older age, and female sex. Diagnosis of the condition is faced with challenges such as nonspecific clinical features and often requires multimodal evaluation including biomarkers, imaging, and biopsy. High-dose corticosteroids remain the first-line treatment; however, steroid-refractory cases are increasingly reported. Promising second-line options include mycophenolate mofetil, antithymocyte globulin, abatacept, and tacrolimus; however, there is a lack of prospective data to support their efficacy. Studies conducted on various preclinical models highlight potential therapeutic targets such as CXCR3.

Conclusion: ICI-M poses a significant challenge in cardio-oncology practice due to its underestimation, high mortality rate, and lack of robust clinical data evaluating standardized screening protocols and second-line treatment measures. Although several second-line agents show promise, the evidence supporting their usage is largely on the basis of expert consensus and case reports, hence representing a strong need for prospective studies offering direct comparisons. Likewise, preclinical studies show great promise in identifying the pathophysiology and potential therapeutic targets for ICI-M; however, translational studies are necessary to validate these findings.

Keywords: Immune checkpoint inhibitors, Immunotherapy, Myocarditis.

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Introduction

With cancer prevalence rising, one of the most groundbreaking advancements in cancer treatment is immunotherapy, which harnesses the body's immune system to target and eliminate malignancies. A key component of this approach is immune checkpoint inhibitors (ICIs), which have demonstrated significant promise in improving patient outcomes.[1]

The US Food and Drug Administration approved ipilimumab, a cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitor, in 2011, marking its first authorization for melanoma therapy.[2] This was followed in 2014 by the approval of nivolumab, a programmed cell death protein-1 (PD-1) inhibitor, with additional agents targeting PD-1 and its ligand PD-L1 introduced in subsequent years.[3,4]

Although immunotherapy is a recent advance in the field of oncology, the concept goes back in time by more than a century. A documented example was the concept of immunosurveillance that was proposed by Ehrlich, postulating that commonly produced malignant cells only progress to develop into clinically significant disease when immunity is compromised.[3]

The anti-CTLA-4 antibody ipilimumab, along with anti-PD-1 agents such as nivolumab and pembrolizumab, has significantly transformed the management of advanced malignancies including metastatic melanoma, lung cancer, and renal cell carcinoma. Despite these therapeutic advances, their mechanism of enhancing immune activation has been associated with a unique spectrum of toxicities termed immune-related adverse events (irAEs). These commonly manifest as gastrointestinal, hepatic, dermatologic, and endocrine complications, including diarrhea, colitis, hepatitis, skin reactions, hypophysitis, and thyroid dysfunction.[5] An increasing number of cases of immune checkpoint inhibitor-related cardiotoxicity began to be reported, with complications ranging from cardiogenic shock to sudden death.[6] A contemporary review of clinical cases noted that the median interval between initiation of ICI therapy and the onset of the first adverse event was 21 days, with the majority of patients receiving treatment with corticosteroids such as prednisolone or methylprednisolone.[7] Due to limited understanding of the disease, there remains a paucity of a standardized treatment protocol.[8]

Due to the lack of awareness of the condition, its nonspecific clinical presentation, overlap with other cardiac and medical pathologies, and diagnostic challenges, the incidence of immune checkpoint inhibitor-related myocarditis (ICI-M) is likely underestimated, which brings us to the point that it is crucial to exercise caution with this manifestation of ICI.[6] Reports suggest an estimated incidence of 0.04%–1.14% among the irAEs,[9,10] and the highest mortality rates among all irAEs of 20–50%.[11]

Not many risk factors contributing to the disease have been identified so far, hence necessitating further review of the topic considering its risk of rapid progression and high mortality rate.[6,10] ICI combination therapy, other anticancer treatment, female sex, preexisting cardiovascular disease, certain tumor types, underlying

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autoimmune pathology, and diabetes mellitus are considered to be contributing factors to the pathogenesis of ICI-M.[12–16] In this review, we primarily focus on the risk factors contributing to the occurrence of ICI-M and various treatment strategies that extend beyond conventional steroid therapy, while also highlighting the current screening and diagnostic methods.

Pathophysiology

Immune checkpoint inhibitors comprise monoclonal antibodies that block suppressive signaling pathways controlling T-cell activity—most notably PD-1/PD-L1 and CTLA-4—thereby strengthening T-cell–mediated antitumor immune responses.[17]

Although the pathophysiology of ICI-M remains unclear, suggested mechanisms include a shared antigen between the tumor and myocardium, T-cell receptor cross-reactivity with a homologous muscle antigen, or T-cell receptors recognizing distinct, unrelated antigens.[18]

Histological findings through cardiac biopsy and autopsy of patients who developed myocarditis following therapy with ICI often reveal skeletal and myocardial T-cell infiltrates showing CD4+, CD8+, and CD68+ cells, with CD20+ B cells being absent. The presence of a shared antigen between the tumor and striated muscle is evidenced by the expression of muscle-specific transcripts in the tumor.[19]

Clinical Features

The clinical features of ICI-M can vary over a wide spectrum ranging from patients being asymptomatic to life-threatening presentations.[11]

Patient presentations can be nonspecific with symptoms and signs like chest pain, dyspnea, elevated troponin and creatine kinase levels, ST-segment elevation, cardiac arrhythmia, and other electrocardiographic abnormalities.[20]

Discussion

Risk Factors

Treatment-related Risk Factors

- *ICI combination therapy*: In a recent review, Yousif et al. highlight the four most prominent risk factors for cardiovascular irAEs. Among them, ICI combination therapy stands out as a major contributor to ICI-M, although shown to successfully overcome cases of primary and secondary resistance to ICIs.[12] Ipilimumab and nivolumab have individually shown remarkable strides in improving survival in melanoma patients, with their combination being an even more successful treatment strategy.[21–24] However, it is the combination of these two agents that is associated with increased reports of adverse effects rather than monotherapy with either one.[23] This is proven by several studies, one of which highlights the difference in incidence of myocarditis in the combined anti-PD1/anti-CTLA4 antibodies group compared to the anti-PD-1 monotherapy group, at 2.4% and 0.5%, respectively.[16] A retrospective study from 2018 utilizing the World Health Organization's (WHO) global database found that myocarditis was reported in 0.41% of cases involving anti-PD-1/PD-L1 therapies (such as nivolumab and atezolizumab), compared to 0.07% for anti-CTLA-4 therapy (such as ipilimumab).[25]
- *Other anticancer treatment*: Other treatment strategies targeting malignancies, including chemotherapy, radiotherapy and tyrosine kinase inhibitors, are being employed to enhance the efficacy of immunotherapy. Nevertheless, their combined use alongside ICIs has proven to increase the likelihood of cardiovascular irAEs.[12] A meta-analysis found that the incidence of cardiovascular irAEs was higher in patients treated with a combination of ICIs and chemotherapy, compared to those receiving ICIs or chemotherapy alone, with incidence rates of 3.7%, 3.1%, and 2.5%, respectively.[26]

Cancer-specific Susceptibility

Tumor Type

Cardiovascular irAEs have been reported more often in patients with melanoma or lung cancer, indicating that the risk of developing these adverse effects might depend on the particular type of tumor. A study involving patients with several cancer types who received at least one cycle of ICIs revealed that the most frequently observed cancer types were lung (35.7%) and melanoma (33.7%). Patients who experienced cardiovascular irAEs within 1 year of starting ICI therapy were more likely to have lung cancer (42.3% vs 34.7%) and less likely to have liver cancer (2.8% vs 6.6%) than those who did not. However, this may represent the more common use of ICIs in these particular types of cancers, potentially leading to over-reporting associated with these malignancies.[27,28]

Host-related Risk Factors

Age and Sex

A recent literature review identifies advancing age (over 64 years) and a high BMI (greater than 28) as possible contributing risk factors of this rare adverse event.[29] Overall, males tend to have a higher risk of developing viral or non-ICI-related myocarditis, while females are generally more prone to autoimmune diseases, indicating a potential susceptibility to ICI-M or cardiovascular irAEs.[30] This observation is further supported by a retrospective study that focused on identifying cardiac complications postinitiation of ICI therapy, where female sex emerged as one of the strongest risk factors, showing a higher overall incidence of cardiovascular irAEs, including cases of pericarditis (2.2%) and atrial fibrillation (2.0%).[31]

Preexisting Autoimmune Disease

Patients with a history of autoimmune disease are generally not included in clinical trial populations, mostly due to fear of exacerbating an already dysregulated immune system.[14] However, the studies that were carried out in this specific cohort have revealed higher occurrences of exacerbations of preexisting autoimmune conditions or irAEs.[15,32,33] It has been hypothesized that patients with preexisting autoimmune diseases involving the heart such as systemic lupus erythematosus, rheumatoid arthritis, sarcoidosis, and Dressler's syndrome may be at a heightened risk for developing cardiovascular irAEs.[34]

Preexisting Cardiovascular Disease

Another notable risk factor in cancer patients undergoing ICI therapy is preexisting cardiovascular disease. According to a meta-analysis, a significant proportion (40%) of individuals who developed cardiovascular irAEs had existing cardiovascular risk factors, with the most common ones being myocardial infarction, peripheral artery disease, and hypertension.[26] A review of the Mayo Clinic database for all patients with cancer who received ICIs evaluated the association of cardiovascular disease with clinical outcomes, and found that 2.4% of the patients developed cardiovascular irAEs. History of heart failure, acute coronary syndrome, and those above the age of 80 years were identified to be factors associated with an increased risk of developing ICI-M.[35]

Metabolic and Inflammatory Conditions

Metabolic disorders such as diabetes mellitus have proven to be independent risk factors that may act as facilitators rather than direct triggers of ICI-M, potentially through mechanisms of chronic inflammation and impaired immune regulation. The logistic regression analysis in a retrospective analysis involving 1,047 participants revealed that

diabetes mellitus [odds ratio (OR): 1.96, 95% confidence interval (CI): 1.05–3.65, $p = 0.034$] was an independent risk factor for ICI-related cardiotoxicity.[36]

Screening Methods

Although no robust monitoring protocol has been standardized for patients receiving immunotherapy, baseline ECG assessment and weekly troponin testing during the first 3 weeks for those receiving combination immunotherapy have been implemented in clinical practice.[18] While it is common to see a rise in cardiac biomarkers (e.g., increased serum troponin levels) secondary to heart tissue damage, nearly 50% of patients exhibit preserved systolic function.[16] Meanwhile, cardiac arrhythmias such as atrial fibrillation, ventricular arrhythmias, and conduction abnormalities are frequently observed, sometimes leading to sudden death.[16,37] ECG and echocardiography can help detect those at risk by flagging up signs such as widening of the QRS complex and narrowing of global longitudinal strain.[17] The simultaneous occurrence of myasthenia gravis and rheumatic and musculoskeletal immune-related adverse events (RMS-irAE) such as myositis after ICI therapy should raise suspicion of myocarditis.[38,39]

Diagnosis

Most cases present with raised troponin levels and abnormal ECGs. Meanwhile, LVEF may be normal.[16]

The diagnosis of ICI-M relies on a multimodal approach due to the variability in its presentation. A definitive diagnosis is based on a combination of the presence of clinical signs, laboratory evidence of myocardial injury, and imaging or histological evidence, while ruling out alternative diagnoses such as ACS and acute infectious myocarditis (Fig. 1).[39]

Cardiac troponin: Elevated levels of troponin are observed in most cases of ICI-M (46–97%), with evidence suggesting that troponin I is more specific to myocardial injury than troponin T.[10]

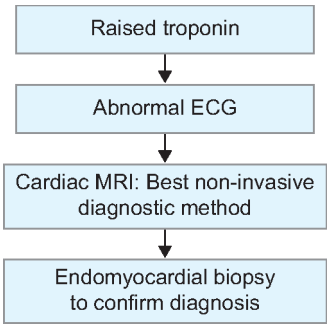

Fig. 1: Flowchart depicting diagnostic methods

Associated symptoms: The onset of new cardiac symptoms alongside musculoskeletal symptoms such as myositis warrants suspicion of ICI-M, possibly due to shared antigenic targets between cardiac and skeletal muscles.[11]

Endomyocardial Biopsy

Endomyocardial biopsy provides a definitive diagnosis of ICI-M, particularly in uncertain cases. EMB typically reveals a characteristic pathology of a T-cell–predominant lymphocytic infiltrate, including CD8+ and CD4+ T cells, along with macrophages, with evidence of nonischemic necrosis occasionally present.[40] However, despite its diagnostic accuracy, EMB is not performed routinely due to its invasive nature and the inherent procedural risks, including cardiac tamponade and myocardial perforation. Moreover, EMB in ICI-M is prone to sampling errors due to the patchy appearance of inflammation in the condition, leading to false negatives when unaffected areas are sampled in the biopsy.[11] To mitigate the risk of false-negative results, recent expert consensus suggests collecting at least three samples of each approximately 1–2 mm and the utilization of preprocedural imaging to guide biopsy location.[40]

Cardiac Imaging

Echocardiogram: ICI-M often presents with new-onset left ventricular impairment. The echocardiogram is widely used as a first-line test in the assessment of left ventricular failure, and while it may aid in the initial evaluation of ICI-M, various studies reveal that LVEF may be preserved in a large proportion of cases of ICI-M, hence limiting its sensitivity as a diagnostic tool.[16,34]

Cardiovascular magnetic resonance: For noninvasive evaluation of myocarditis, cardiac magnetic resonance (CMR) imaging is widely accepted as the reference standard. It is highly valuable in the diagnosis of ICI-M owing to its high tissue specificity and minimal procedural risk, allowing detection of myocardial edema and nonischemic patterns of myocardial injury, including necrosis and scarring.[41]

The updated 2018 Lake Louise (LL) criteria underpin the CMR diagnosis of ICI-M, necessitating evidence of myocardial edema on T2-weighted imaging alongside a T1-based feature of nonischemic injury [late gadolinium enhancement (LGE) or increased extracellular volume (ECV)].[42]

In one internal registry, the criteria reflecting nonischemic myocardial injury (T1-based markers, including LGE, T1, or ECV elevation) were met by 95% of patients with proven ICI-M, whereas only 51% of patients met the T2-based criteria for myocardial edema.[43]

In a more recent cohort study, LGE, which represents nonischemic patterns of myocardial injury, was observed far more frequently in ICI-M patients when compared to pre-ICI-M control groups (82% vs 10%). However, LGE was detected less frequently in ICI-M when compared to viral myocarditis (82% vs 100%). Conversely, T2 mapping results, which represent myocardial edema, were only present in 24% of patients.

Notably, ICI-M exhibits distinct patterns of LGE localization in the septal and midwall layers, in contrast to viral myocarditis. In the same study, 48% of ICI-M patients showed septal LGE compared to 29% of those with viral myocarditis, while midwall LGE was observed in 33% and 2%, respectively. The presence of septal LGE in particular is associated with an increased incidence of major adverse cardiovascular events.

Although CMR is the best noninvasive diagnostic modality for ICI-M, patients with ICI-M show a lower rate of fulfillment of the 2018 LL criteria, with only 61% of patients with ICI-M meeting both criteria.[44] Given the unique imaging patterns and diagnostic limitations of LL in ICI-M, specialized CMR criteria may be necessary, and patients should be treated for ICI-M if any single criterion is met in the context of high clinical suspicion.

Treatment

First-line Treatment

Despite its relative rarity, the mortality associated with ICI-M is an astounding 50%, warranting the need for more effective treatment regimens in place.[45]

Specific treatments for ICI-M are rare, and there are no definitive treatment protocols in place. The American College of Cardiology recommends immediate discontinuation of the ICI and initiation of high-dose intravenous methylprednisolone (1 gm daily) for 3 days followed by tapering to oral prednisolone (1–2 mg/kg/day) for confirmed or suspected ICI-M.[46]

Steroid-resistant and Steroid-refractory ICI-myocarditis

Steroid-refractory ICI-M refers to ICI-M which fails to demonstrate clinical improvement or biochemical response to high-dose corticosteroids within 24–72 hours of its commencement. Steroid-resistant is sometimes used as an interchangeable term with steroid refractory but mostly refers to ICI-M which initially responds to corticosteroids but relapses or worsens during the phase of steroid tapering.[8] The high

incidence of steroid-refractory and steroid-resistant cases of ICI-M suggests that isolated steroid therapy alone is not sufficient in the effective treatment of ICI-M.

Second-line Immunosuppressive Agents

Mycophenolate mofetil: It is considered a reasonable option for steroid-resistant or steroid-refractory ICI-M on the basis of expert consensus and its efficacy in other immune-related cardiac conditions. Mycophenolate Mofetil inhibits inosine monophosphate dehydrogenase, thereby blocking *de novo* purine synthesis in T and B lymphocytes, hence inhibiting lymphocyte proliferation.[47] A prospective cohort study by Blagova et al., evaluating the role of a combination of mycophenolate mofetil with steroids in the treatment of lymphocytic myocarditis, revealed a high efficacy comparable to the standard combination of steroids and azathioprine, but with improved tolerance levels and far fewer infectious complications. Extrapolating the findings of this study would suggest its potential therapeutic benefits in the treatment of ICI-M.[48]

Tacrolimus: A calcineurin inhibitor that acts on IL-2 expression and inhibits T-cell differentiation and growth; it has proven to be efficacious in the instance of corticosteroid-refractory ICI-M in a few case studies; it is often combined with IVIG, which plays a role in T-cell downregulation (via IL-33 and prostaglandin E-2).[44]

Antithymocyte globulin (ATG): ATG is a second-line T-cell-depleting immunosuppressive agent which is recommended based on expert consensus by the American Heart Association for steroid-refractory/resistant ICI-M. The rationale for its use is supported by the pathophysiological similarities between ICI-M and acute cellular rejection in cardiac transplantation, in which T-cell-targeted therapies such as ATG are employed. The use of ATG is associated with an increased risk of infection and should ideally be supervised by a cardiac transplant team.[49]

Case reports and case series have revealed successful use of ATG in fulminant steroid-refractory ICI-M and are a promising therapeutic avenue, particularly in hemodynamically unstable patients.[50,51]

IVIG and Plasmapheresis

Plasmapheresis and IVIG therapy are beneficial options in patients presenting with associated neuromuscular complications such as myasthenia gravis.[52] The American College of Cardiology in its 2024 Expert Consensus Decision Pathway states that IVIG may be considered in autoimmune myocarditis, including ICI-M, when viral infections have been excluded by endomyocardial biopsy of samples.[46]

Biologic Agents

TNF-alpha Antagonists

TNF-alpha antagonists, such as infliximab, are recommended for refractory or steroid-resistant myocarditis based on anecdotal evidence; however, the empirical evidence base supporting their use remains weak. Infliximab is typically contraindicated in moderate to severe heart failure, and Liu et al. reported clinical data from 18 cases where infliximab was used; while 66.7% of patients experienced improvement, 55.6% died (22.2% from cardiovascular causes), hence suggesting concerns regarding its safety profile in patients with heart failure. However, the evidence is insufficient to conclude that infliximab definitively worsens heart failure in ICI-M.[53]

Abatacept

Abatacept is a CTLA-4 Ig Fusion Protein which targets T-cell costimulation and has shown promising outcomes in preclinical models and case reports.[53]

In particular, it is noted to be efficacious in myocarditis associated with myositis; however, there is a potential risk of tumor relapse noted with the usage of abatacept, as described in the instance of two patients who developed tumor relapse following treatment with abatacept. Hence, prospective clinical trials are necessary to evaluate its overall efficacy and safety profile.

The ATRIUM trial is a phase 3, randomized, placebo-controlled study evaluating abatacept (10 mg/kg IV at baseline, 24 hours, and day 14, with an optional dose at day 28) in hospitalized patients with ICI-M, with the primary endpoint being reduction in major adverse cardiac events (MACE). The trial is actively recruiting and has not released interim or final results (Table 1).[54]

Other Biologic Agents

Other biologic agents that target T-cells, such as alemtuzumab (CD52 antibody) and tocilizumab (IL-6 inhibitor), are also currently promising investigative second-line options that are potentially effective in ICI-M. However, the use of other biologic agents requires further RCTs to substantiate their mortality and morbidity benefits.[52,53,55]

Promising Therapeutic Avenues in Preclinical and Translational Models

CXCR3-CXCL9/10

An animal model study conducted in 2020 evaluated the role of immunoproteasome in the development of ICI-M and provided translational evidence that immunoproteasome inhibitors such as ONX

Table 1: Treatment modalities beyond steroids

Agent	*Mechanism/rationale for use*	*Evidence*
Mycophenolate mofetil (MMF)	A selective Inhibitor of Inosine Monophosphate dehydrogenase, essential for B and T cell proliferation	Use supported by efficacy in cardioallograft rejection and virus-negative lymphocytic myocarditis[47,48]
Tacrolimus	T-cell targeted immunosuppressive agent, often used in conditions such as giant cell myocarditis	Used successfully in two steroid-refractory cases of ICI-M alongside IVIG[45]
Abatacept (CTLA-4 agonist)	CTLA-4 immunoglobulin fusion protein that binds to CD80/CD86 leading to T-cell anergy	Successfully used in steroid-refractory cases, particularly those with concurrent myositis.[30] ATRIUM trial currently ongoing[52]
Infliximab (TNF-α Inhibitor)	Blocks TNF-α, a pro-inflammatory cytokine	Recommended by guidelines such as ASCO, typically contraindicated in moderate to severe heart failure. The existing evidence based on case series is insufficient to conclude that infliximab worsens heart failure in ICI-M[55]
Antithymocyte globulin (ATG)	Targets T-cells by depletion and inducing apoptosis	Successfully used in cases of fulminant myocarditis refractory to steroids. Carries inherent risk of infectious disease.[50,51]
Intravenous immunoglobulin (IVIG)	Immunomodulatory effects including neutralizing pro-inflammatory cytokines	Used successfully in cases of steroid-refractory ICI-M along with Tacrolimus.[45] Considered to be efficacious in patients with concurrent neuromuscular toxicities[54]

0914 are able to mitigate autoimmune cardiac damage and are a potential therapeutic option beyond corticosteroids and could serve a role in the cases of refractory myocarditis due to ICIs. The study identified the CXCR3-CXCL9/10 axis as a key therapeutic target; hence, blockade of CXCR3 or depletion of these macrophages reduced pathogenic T-cell infiltration and, hence, disease outcomes.[56]

IL-15 supplementation:

A study by Yu et al. in 2024 used both human samples and an in vivo mouse model to evaluate the roles of IL-15 supplementation and CD4+ T cells in the treatment and pathogenesis of ICI-M. They observed in the human samples that ICI-M was associated with a marked reduction in CD4+ TCM and that as myocarditis severity increased, there was a corresponding decrease in IL-15 levels. The animal model of mice with ICI-M also revealed evidence of decreased CD4+ T_{CM} cells and associated cardiac fibrosis. Supplementation with IL-15 in mice resulted in increased CD4+ T_{CM} cells and a reduction in cardiac fibrosis.[57]

Conclusion

Although ICIs are revolutionizing cancer therapy, they come with their own set of adverse side effects, one of the most fatal being myocarditis, which is probably underestimated and shown to have the highest mortality rates among all irAEs. We identified a paucity of robust clinical data evaluating standardized screening protocols and second-line treatment measures. Risk factors dependent on the type of cancer treatment include the use of ICI combination therapy and use of other anticancer therapy, with the former being the most recognized contributor to the pathology. Other important factors posing risk that are patient-specific include preexisting cardiovascular disease, preexisting autoimmune disease, and the tumor type. For steroid-resistant or refractory cases of ICI-M, second-line agents have shown positive outcomes, but use of these is dependent on expert consensus and individual case reports, hence indicating a stronger need for prospective studies offering direct comparisons. At the same time, pre-clinical studies have been successful in identifying potential therapeutic targets for ICI-M while still needing validation from translational studies.

Ethical Statement

This study is a narrative review based on previously published literature and does not involve any new studies with human participants or animals. Hence, approval from an institutional ethics committee and a protocol number are not applicable. The manuscript complies with relevant ethical standards.

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