Cancer Treatment Reviews 100 (2021) 102282

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevier.com/locate/ctrv

Pathophysiology, diagnosis and management of cardiac toxicity induced by immune checkpoint inhibitors and BRAF and MEK inhibitors

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ARTICLE INFO

Keywords:
Cardiotoxicity
Myocarditis
Heart failure
Hypertension
Immune checkpoint inhibitors
Pathophysiology
Immune related adverse events
BRAF inhibitor
MEK inhibitor
Melanoma

ABSTRACT

Immune checkpoint inhibitors (ICIs) and BRAF and MEK inhibitors (BRAFi/MEKi) have drastically improved the outcome of melanoma patients. ICIs can induce myocarditis, a rare immune related adverse event (irAE) with an estimated lethality of 50%. BRAFi/MEKi may induce left ventricular ejection fraction decrease, hypertension or QT interval prolongation. While the BRAFi/MEKi induced cardiotoxicity is often reversible upon treatment discontinuation or dose adaptation and symptomatic therapy is often sufficient to restore cardiac function, the treatment of ICI-induced myocarditis mainly relies on high dose corticosteroids. There is no established therapy for steroid resistant myocarditis, yet various drugs have been reported to improve outcome. Shared epitopes between melanoma cells and cardiac tissue are thought to underlie the development of ICIs induced myocarditis. The mechanism of BRAFi/MEKi induced cardiotoxicity appears to be related to the Ras-Raf-MEK-ERK pathway in cardiomyocyte repair, survival and proliferation. With the emerging application of ICI-BRAFi/MEKi combinations, so called triplet therapies, differentiating between these two types of cardiotoxicity will become important for appropriate patient management.

In this article we provide a summary of the existing literature on the pathophysiology, diagnosis and management of cardiotoxicity of melanoma therapies.

Background

The introduction of immune checkpoint inhibitors (ICIs) and tyrosine kinase inhibitors (TKIs) in 2011 has drastically changed the landscape of melanoma therapy [1]. The monoclonal antibody ipilimumab inhibiting the immune checkpoint cytotoxic T lymphocyte antigen 4 (CTLA-4) was the first drug to improve overall survival compared with the prior standard of care chemotherapy [2]. Subsequently, the antibodies nivolumab and pembrolizumab targeting programmed cell death 1 (PD-1) were approved. Currently, the combination of ipilimumab and nivolumab induces a durable disease response in 45–50% of metastatic melanoma patients [3]. Anti-PD1 antibodies as adjuvant therapy in patients with resected stage III or IV melanoma significantly improve relapse-free survival [4,5].

However, this effectiveness comes at the price of a high rate of immune-related adverse events (irAEs), with severe grade 3–4 irAEs occurring in 60% of patients treated with ipilimumab and nivolumab, which may potentially affect any organ [6]. With an estimated incidence of around 1%, cardiovascular irAEs are rare but have drawn considerable attention over the recent years because of a high risk of mortality [7,8]. Many types of cardiac irAEs have been reported including ICI-induced myocarditis, pericarditis, vasculitis, supraventricular arrhythmias, cardiac conduction disturbances, acute coronary syndromes, stress cardiomyopathy [9] , valvular heart disease, asymptomatic left ventricular function impairment and isolated troponin elevation [10]. With an estimated mortality rate of 50%, myocarditis remains the most feared cardiac irAE [10].

Nearly half of the melanoma patients harbor a mutation in the BRAF gene, most commonly the BRAF valine to glutamine point mutation

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https://doi.org/10.1016/j.ctrv.2021.102282
Received 11 May 2021; Received in revised form 11 August 2021; Accepted 12 August 2021
Available online 18 August 2021

Abbreviations

ICI	Immune checkpoint inhibitors
BRAFi/MEKi	BRAF and MEK inhibitors
TKIs	tyrosine kinase inhibitors
CTLA-4	cytotoxic T lymphocyte antigen 4
PD-1	programmed cell death 1
irAEs	immune-related adverse events
LVEF	left ventricular ejection fraction
CMR	Cardiac magnetic resonance
PET-CT	positron emission tomography-computed tomography
ECMO	extracorporeal membrane oxygenation

(V600E). This mutation leads to constitutive activation of the downstream MEK/ERK pathway and largely contributes to the pathogenesis of the disease [11]. TKIs targeting BRAF and MEK1/2 in metastatic or unresectable disease induce a rapid response in about 70% of the cases [12,13] and decrease relapse risk in resected stage III BRAF mutant melanoma [14]. Several trials showed that combining a MEK1/2 inhibitor (MEKi) with a BRAF inhibitor (BRAFi) offers superior response rates, progression free survival and overall survival compared to single agent BRAFi where compensatory MEK hyperactivation is associated with treatment resistance [12,13,15]. There are currently three approved BRAFi/MEKi combinations: vemurafenib and cobimetinib, dabrafenib and trametinib, and encorafenib and binimetinib [13,16]. The main cardiac toxicities induced by BRAFi/MEKi are left ventricular ejection fraction (LVEF) decrease, hypertension, and QT interval prolongation [17,16]. Importantly, most adverse events are class effects rather than substance specific effects and the toxicity profile thus largely overlaps between the approved combinations, with minor exceptions [18,19].

Most recently published reviews on cardiovascular toxicities induced by anticancer therapies, including ICIs, have mainly focused on diagnosis and management [20–23]. In the present article we will first provide an overview of the relevant literature on the underlying pathophysiological mechanism of cardiac toxicity induced by ICIs and BRAFi/MEKi. We will then discuss the clinical adverse events associated with ICI focusing on myocarditis, and with BRAFi/MEKi focusing on (LVEF) decrease and hypertension, and suggest an interdisciplinary approach including oncologists and cardiologists with an emphasis on the role of cardiac imaging to improve early diagnosis and management of patients at risk of developing potentially fatal irAEs.

Pathophysiology of ICI related cardiac toxicity

Immune checkpoints are inhibitory signaling pathways which regulate the duration and amplitude of physiological immune responses [24]. This mechanism is essential to maintain self-tolerance and to avoid an excessive immune activation in the presence of an antigen, protecting tissues from damage. The dysregulated expression of immune checkpoints by cancer cells allows the latter to evade immune detection and destruction [24]. ICIs targeting the PD1/PDL1 and CTLA4/B7 checkpoints remove this “break” on the immune system and induce a T-cell response directed against tumor antigens.

Despite an increasing number of reports on ICI-related cardiovascular events, the underlying pathophysiological mechanism remains poorly investigated. Under physiological conditions, CTLA-4 and PD-1, both members of the CD-28 regulatory cells surface receptor family play key roles in the regulation of T cell responses in the myocardium, protecting the heart against T-cell mediated injury [25–27].

A handful of animal models of ICI-related cardiotoxicity have been published, providing limited, yet incremental knowledge on this potentially fatal irAE. In the cMy-mOVA model of myocarditis, where transgenic OVA is expressed in cardiac myocytes under the control of the α-myosin H chain promoter, adoptive transfer of PD-1 (-/-) CD8 + T cells, compared to PD1 (+/+) CD8 + T cells, induced increased disease activity and enhanced myocardial inflammatory cells infiltrate including neutrophils. In addition, enhanced proliferation *in vivo,* and increased cytotoxic activity of PD-1 (-/-) T lymphocytes against myocardial endothelial cells *in vitro* were observed [25]. In experimental autoimmune myocarditis, a model dependent on CD4 + T cells in which myocardial inflammation was caused by immunization in BALB/c mice with a peptide of the murine α-myosin H chain, PD-1 deficient mice presented higher disease activity compared to wildtype mice. This finding was associated with increased inflammatory cell infiltration mainly composed of neutrophils but also of CD8+, CD4 + T cells and macrophages and enhanced secretion of serum markers of myocardial damage such as troponin I [25].

Most interestingly, PD-1 (-/-) BALB/c mice develop severe dilated cardiomyopathy with decreased ventricular function and sudden cardiac death due to heart failure. Affected hearts did not show any immune cell infiltration but diffuse deposition of complement C3 and immunoglobulin G (IgG) on the surface of cardiomyocytes. These high-titer autoantibodies were identified as specific against cardiac troponin I, a subunit of the troponin complex, which plays an essential role in regulating excitation–contraction coupling in the heart [28,29,30].

In MRL mice, which are genetically predisposed to systemic autoimmunity, PD-1 deficiency induced a fatal lymphocytic myocarditis, which is reminiscent of CTLA-4-deficient mice [26]. The hearts of MRL-PD-1 (-/-) mice exhibited an extensive infiltration of CD4 + and CD8 + T cells and myeloid cells [31]. Notably, the frequency of myocarditis was slightly lower (96% vs 100%) in PD-1 (-/-) mice, and in contrast with CTLA-4 (-/-) mice, no polyclonal activation of lymphocytes was observed. Thus, a non-specific activation of CD4 + T cells is observed in CTLA-4 (-/-) mice with invasion of multiple organs while the cardiotoxicity in PD-1 (-/-) mice is mediated by an antigen-specific autoimmune response. Moreover, high-titer auto-antibodies directed against cardiac myosin, a major sarcomeric protein, have been reported in PD-1 (-/-), but not in CTLA-4 (-/-) mice, further supporting this hypothesis [31,26].

A non-human primate model of ICI related myocarditis using female cynomolgus monkeys was recently reported. Five animals were treated with ipilimumab (15 mg/kg) and nivolumab (20 mg/kg) weekly for four doses and the necropsy findings compared to two animals treated with saline. Marked inflammation was present in numerous tissues of the ICI-treated monkeys compared to minimal infiltrates found in some tissues in control monkeys. A prominent, multifocal infiltration of CD4 + and CD8 + T cells, lower numbers of macrophages and occasional B cells was found in the myocardium with minimal cardiomyocyte degeneration/necrosis as well as increased cardiac troponin I and NT-pro-BNP [32]. These findings are similar to those described in endomyocardial biopsies of patients presenting with ICI related myocarditis [7]. In addition, in autopsy samples of 2 patients treated with ipilimumab and nivolumab for metastatic melanoma who developed lethal fulminant myocarditis, Johnson et al. reported that selective clonal T-cell populations infiltrating the myocardium were identical to those present in the tumor and in the skeletal muscle [7]. Interestingly, high levels of muscle-specific desmin and troponin antigens were also found in the melanoma lesions of both patients [7].

In the light of these few studies, the current main hypothesis on the pathophysiology of ICI-related cardiotoxicity is that muscle specific antigens, e.g against troponin, myosin or desmin, are shared between the tumor and cardiomyocytes, triggering a crossed reaction with T cells targeting both the tumor and the cardiac muscle. This hypothesis is supported by findings from non small cell lung cancer patients who presented with skin toxicity under anti-PD1 treatment where nine T cell antigens shared between tumor tissue and skin were identified [33] (Fig. 1).

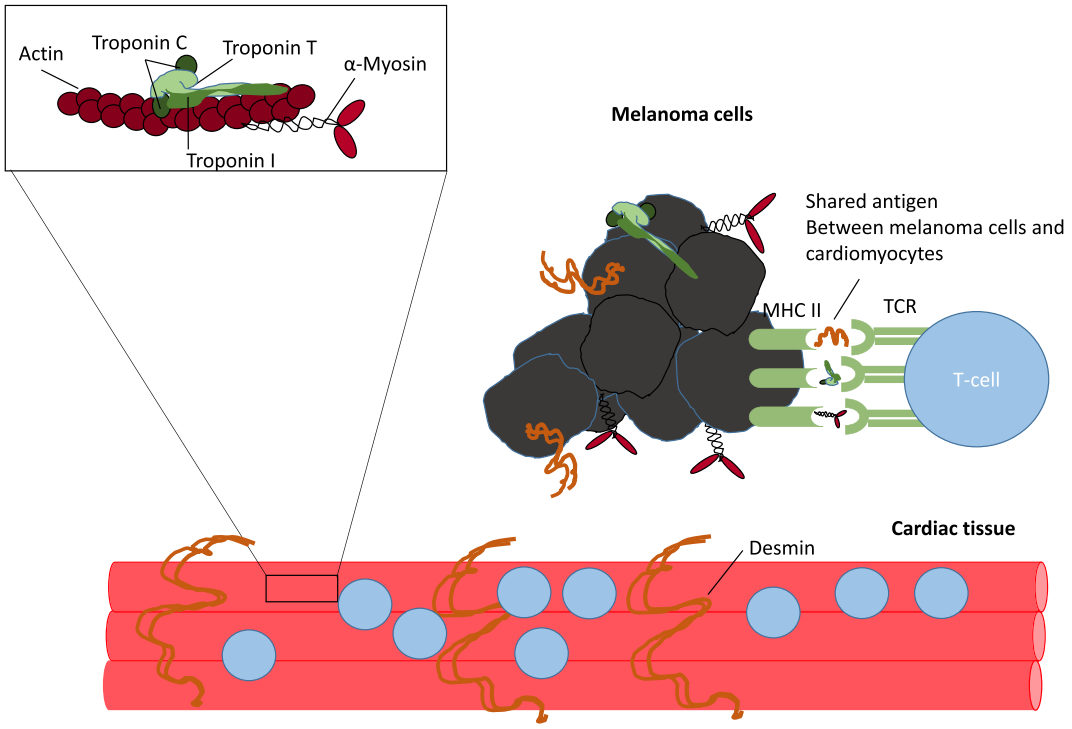

Fig. 1. Pathophysiology of immune checkpoint inhibitor induced cardiotoxicity. The presence of shared epitopes such as troponin, desmin and myosin a-chain between melanoma cells and cardiac tissue triggers myocarditis. TCR; T cell receptor.

Diagnostic work-up of suspected ICI related cardiotoxicity

The heterogeneity in clinical presentations and the potentially rapidly fatal evolution, markedly complexifies the diagnostic process of ICI-related myocarditis. The initial clinical examination may be misleading and may resemble the presentation of the more common viral myocarditis [7,34]. Asthenia, dyspnea, or even an isolated serum troponin elevation may be the only initial manifestations, exposing to the risk of diagnostic delay. ICI-related myocarditis can also mimic acute coronary syndrome in case of chest pain with troponin elevation, or manifest as acute congestive heart failure, or even cardiogenic shock [22]. Syncope, lipothymia, or palpitations may be the manifestation of supraventricular and/or ventricular arrhythmias, or high degree conductive disorders. It is of utmost importance to bear in mind that multiple organ toxicities may affect a single patient, notably in patients under combined CTLA-4 and PD-1 blockade. For instance, cardiac arrhythmia can be caused by myocarditis, but may also be the result of ICI-induced thyrotoxicosis. Likewise, myositis may also induce a mild troponin elevation, even in the absence of a cardiac involvement [35,21]. Rarely, myocarditis may be associated with both ICI-induced myositis and myasthenia gravis further complexifying the diagnostic process and emphasizing the necessity of a joint approach between oncologists and various organ specialists [36]. Most cases of ICI-induced myocarditis occur within 3 months following ICI therapy initiation [10]. In two retrospective analyses cardiotoxicity was diagnosed at a median of 30 days (IQR 18–60 days) [10] and 65 days (range, 2–454 days) [37], respectively. However, it is essential to emphasize that cardiac irAEs may occur at any time even at a later stage of the treatment. To date, only the use of a combination of ICI has been identified as a risk factor for myocarditis [10,38].

The diagnosis of ICI related myocarditis requires an interdisciplinary approach, relying on a body of clinical, biological and cardiac imaging evidence. Endomyocardial biopsy remains indicated in selected cases as the gold standard examination. The implication of cardiologists, preferably with experience in cardio-oncology and in advanced cardiac imaging is critical as soon as ICI-related myocarditis is suspected. An ECG, a troponin T dosage and a transthoracic cardiac ultrasound are indicated as a first-line exploration. The ECG was reported to be abnormal in up to 86% with myocarditis and may reveal unspecific modifications such as conduction or rhythm disturbance, or repolarization abnormalities [39]. In most cases, the troponin level is increased, raising an important differential diagnosis with acute coronary syndrome depending on the patient's cardiovascular risk profile. Therefore, an assessment of the coronary status is often required, either through coronary angiography or coronary CT angiography [40].

The creatine kinase (CK) dosage is essential in order to exclude a concomitant myositis, which is found in almost 25% of cases [8]. A troponin I dosage could also prove useful in in the presence of peripheral myositis as it is more specific of the myocardium than troponin T. Indeed, an increase in troponin T level, also found in the skeletal muscle, may be observed in case of myositis without associated myocarditis [41].

Echocardiography is a first-line test and may reveal left ventricular wall motion abnormalities, increased myocardial wall thickness, impaired left and/or right ventricular functions. Ventricular dilation is usually absent in the acute phase of myocarditis [42]. The presence of a pericardial effusion suggests the diagnosis of pericarditis, but its presence is not necessary nor sufficient to retain the diagnosis of associated myocarditis. Thus, it may occur as isolated pericarditis or with coexisting myocarditis [37]. It is worth emphasizing that a normal ECG does not rule out the diagnosis of myocarditis, and a normal initial echocardiography does not exclude the risk of progression toward fulminant myocarditis. In fact, in a recent report on 103 cases of ICI related myocarditis by Zhang et al., 60% of the patients did not have any left ventricular ejection fraction (LVEF) impairment [43].

Cardiac magnetic resonance (CMR) imaging is also indicated in case of suspected myocarditis and may reveal myocardial edema through T2-based markers and/or myocardial injury through T1-based markers (including the presence of late gadolinium enhancement following a non-ischemic distribution), which, in combination, have high diagnostic accuracy for the diagnosis of myocarditis [44]. In a retrospective study from a large international registry including 136 patients,

Thavendiranathan P et al. found that higher myocardial T1 values were independently associated with the development of major adverse cardiovascular events [45]. They also observed that T1 and T2 values were increased in respectively 78% and 43% of patients with ICI-related myocarditis, and that patients with abnormal T1 values were more often symptomatic and had decreased LVEF. CMR will also provide an accurate assessment of LV volumes, ejection fraction and regional wall motion abnormalities, and may detect pericardial inflammation or effusion, which are important supportive signs in case of suspected myocarditis. However, in the setting of suspected ICI-related myocarditis, late gadolinium enhancement was found in only 48% of the patients undergoing a CMR in the population analyzed by Zhang et al. [43]. For patients with contraindication to CMR, myocardial inflammation may also be revealed by positron emission tomography-computed tomography (PET-CT) using 18F-FDG [46,47,48] or 68 Ga-DOTATOC [49].

An endomyocardial biopsy is recommended when the diagnosis of ICI-related myocarditis remains questionable despite the initial diagnostic work-up and when the diagnosis has implications on the decision to pursue ICI therapy, which is often the only treatment that may improve the patient's cancer-related prognosis [50]. The common findings of the histopathology analysis of ICI-related myocarditis associate an abundant lymphocytic or lymphohistiocytic myocardial infiltration of CD4 + and CD8 + T-cells, as well as a CD 68 + macrophages infiltration [7]. It has also been reported that compared with acute cellular rejection, ICI-related myocarditis is characterized by a more lymphohistiocytic infiltration with an increased CD68/CD3 ratio and in the proportion of PD-L1 + macrophages and myocytes [51]. Thus, intense PDL1 staining of inflammatory cells and cardiomyocytes in the inflammatory foci has been suggested as a specific feature of ICI-induced myocarditis [52]. However, it is worth mentioning that, from a histopathological perspective, precisely distinguishing an ICI-related myocarditis from another cause, including viral myocarditis, may prove an arduous task. Therefore, histopathological findings should always be interpreted in the light of the clinical context. The endomyocardial biopsy should be performed as early as possible, ideally before the introduction of immunosuppressive treatments, as these could interfere with the results of the pathological examination. However, given the low sensitivity [53] and the small risk of cardiac perforation [7,54] it should be reserved for selected cases where the results will have a strong impact on patient's management. For instance, in BRAF wild-type metastatic melanoma patients without any alternative therapy option other than ICI, myocarditis needs to be confirmed before definitely stopping ICI. Interestingly, an endomyocardial biopsy grading system has been recently proposed [52]. In this study, patients with low grade myocardial inflammation (Grade 1) strikingly continued ICI without any adverse cardiovascular events during follow-up.

The results of all diagnostic tests performed should be integrated by the multidisciplinary cardio-oncology team to make the final clinical diagnosis of myocarditis. A diagnostic framework has been proposed by Bonaca et al, which defines definite, probable or possible ICI-related myocarditis based on the result of the different diagnostic tests [55].

Management of ICI related cardiotoxicity

Considering its high mortality rate, all patients with clinically confirmed ICI-related myocarditis need to be hospitalized in an intensive care unit and continuous monitoring of the ECG tracing is immediately required because of an increased risk of ventricular arrhythmia and/or cardiac conduction disturbance [23]. A reassuring and stable clinical condition on admission does not preclude a fulminant evolution afterward, further emphasizing the necessity of an initial hospitalization in an intensive care unit. Following ICI suspension, the administration of immunosuppressants and the symptomatic management of heart failure represent the cornerstone of the therapeutic strategy. High dose intravenous corticosteroids are the first-line therapy as soon as the diagnosis of myocarditis is retained. We recommend the administration of methylprednisolone at a minimum dosage of 2 mg/kg/day, and up to 1000 mg/day in case of severe myocarditis. After 3 days of intravenous therapy, a dose reduction to 1 mg/kg/day of oral prednisone can be considered with a gradual dose decrease over 4 to 6 weeks, depending on the evolution of the clinical symptoms and serum markers such as troponin T and troponin I [23]. The clinical evolution during the acute treatment phase should be closely monitored using ECG, troponin levels and echocardiography. Myocardial edema detected by CMR generally tends to decline after 4 weeks from the symptom onset [56]. Follow-up CMR may be useful from a prognostic point of view to ascertain the disappearance of oedema and to assess the extent of myocardial necrosis; it is generally performed 6 to 12 months after the index event [57] but may be performed earlier depending on the severity of the initial acute event and the clinical evolution.

In case of unfavorable evolution, intensification with various immunosuppressive drugs [58] have been reported in the literature including the CTLA-4 agonist abatacept [59], alemtuzumab [60], tacrolimus [34], tocilizumab [49], mycophenolate mofetil, infliximab, intravenous immunoglobulins, plasmapheresis or antithymocyte globulin [61]. In a case control study, of all the above mentioned therapies, infliximab was associated with a significantly higher risk of death from cardiovascular causes [58]. The current level of evidence to favor one treatment over another remains limited.

It needs to be emphasized that the simultaneous symptomatic management of heart failure is essential. Depending on the clinical status and the oncological prognosis, escalation of therapy toward hemodynamic support with catecholamines, or even circulatory assistance with extracorporeal membrane oxygenation (ECMO) may be temporarily implemented, pending an improvement in cardiac function. The occurrence of definite ICI related myocarditis currently definitively contraindicates any reintroduction of ICI therapy thereafter (Fig. 2).

Pathophysiology of BRAF/MEK inhibitor related cardiotoxicity

Cardiovascular adverse events induced by BRAFi/MEKi are rare but potentially life-threatening and need to be monitored. In phase 3 clinical trials, reduction in LVEF of any grade was reported in 5.7–11.7%, hypertension in 10.9–29.4% and QT interval prolongation in 0–4.5% of the patients treated with BRAFi/MEKi depending on the combinations used [19]. In a recent *meta*-analysis of the five pivotal randomized clinical trials including over 2300 patients, combined BRAFi/MEKi therapy was associated with a higher relative risk of LVEF decrease, hypertension and pulmonary embolism as compared to BRAFi monotherapy [62]. Grade 3–4 reduction in LVEF (LVEF $<$ 40% or LVEF reduction $>$ 20% compared to baseline) was found in 8% of the patients treated with a BRAFi/MEKi combination, and patients aged $<$ 55 years were at significantly higher risk of LVEF reduction. While QT interval prolongation is more often observed under BRAFi, MEKi are more frequently associated with LVEF decrease. Trametinib seems to be particularly associated with a LVEF decrease [19,62] (Table 1). Of note, MEKi-induced cardiotoxicity is in most cases asymptomatic, often uncovered during a systematic follow-up echocardiographic examination and reversible after treatment interruption.

When activated under physiologic circumstances, the Ras kinase mainly induces the Raf-MEK-ERK signaling cascade. In turn, these molecular events lead to the transcription of large networks of genes essentially involved in cell proliferation, differentiation and survival [63,64].

Several studies showed the importance of the Ras-Raf-MEK-ERK pathway in cardiomyocyte repair, survival and proliferation *in vitro* [65–68]. The autophosphorylation of ERK 1/2 on Thr188 was shown to direct ERK1/2 to phosphorylate nuclear targets known to cause cardiac hypertrophy [68]. In transgenic mice, cardiac specific overexpression of Erk2 ^{T188D} (gain of function Erk2) did not induce any morphological changes. However, when transverse aortic constriction was used to

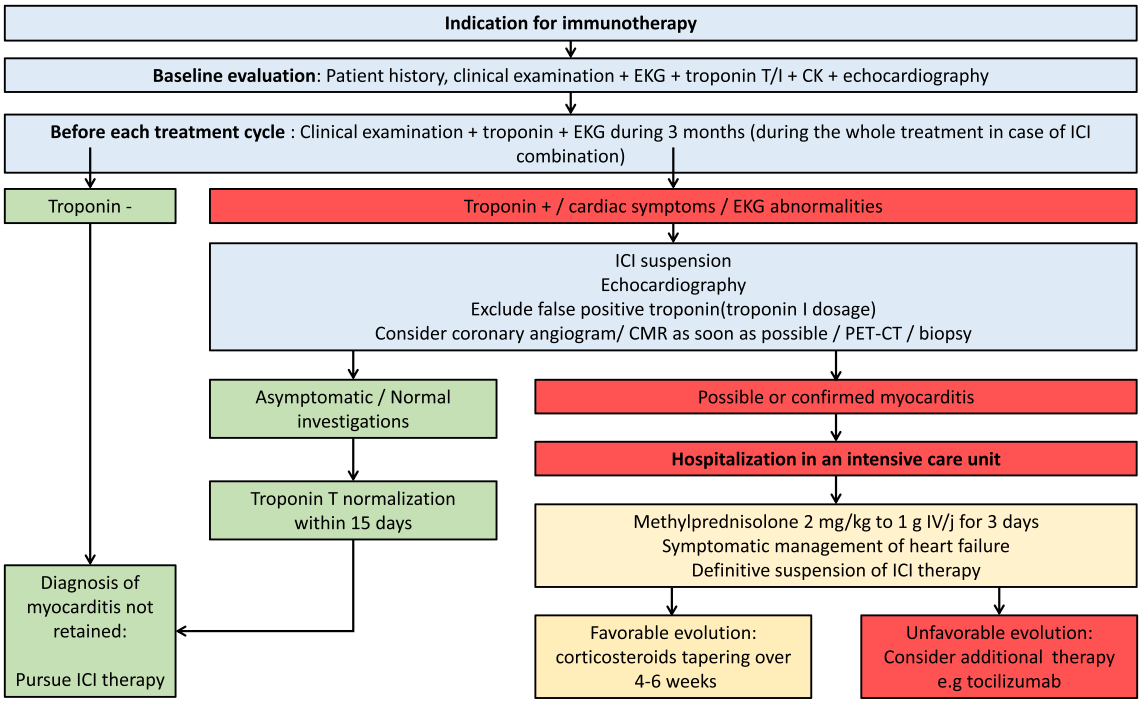

Fig. 2. Proposed algorithm for diagnostic workup and management of immune checkpoint inhibitor induced myocarditis.

Table 1
Incidence of QTc prolongation, hypertension and left ventricular ejection fraction decrease in major BRAFi/MEKi trials.

Clinical trial/ Reference	Study arm	QTc prolongation all grade (%)	QTc prolongation > grade 3 (%)	Hypertension all grade (%)	Hypertension > grade 3 (%)	LVEF decrease all grade (%)	LVEF decrease> grade 3 (%)
COMBI-d [86]	Dabrafenib + Trametinib	0	0	25	6	8	2
	Dabrafenib + Placebo	2	<1	14	5	3	2
COMBI AD [14]	Dabrafenib + Trametinib	Not reported	Not reported	11	6	Not reported	Not reported
	Placebo	Not reported	Not reported	8	2	Not reported	Not reported
COMBI-v [15]	Dabrafenib + Trametinib	Not reported	Not reported	26	14	8	4
	Vemurafenib	Not reported	Not reported	24	9	0	0
CoBRIM [87]	Vemurafenib + Cobimetinib	5	1	16	6	12	2
	Vemurafenib + Placebo	5	1	8	3	5	1
COLUMBUS [13]	Encorafenib + Binimetinib	Not reported	Not reported	11	6	6	1
	Encorafenib	Not reported	Not reported	6	3	2	1
	Vemurafenib	Not reported	Not reported	11	3	1	0
IMspire150[84]	Atezolizumab + Cobimetinib + Vemurafenib	Not reported	Not reported	Not reported	Not reported	Not reported	0.4
	Placebo + Cobimetinib + Vemurabienib	Not reported	Not reported	Not reported	Not reported	Not reported	1.2

induce hypertrophy, an increase in morphological and echocardiographic ventricle thickness, heart weight and cardiomyocyte size was detected in *Erk2* ^{T188D} transgenic animals compared to wildtype or phosphorylation deficient Erk2 mice undergoing transverse aortic constriction [68].

These observations are supported by evidence originating from studies performed on transgenic mice with cardiac-restricted expression of activated MEK1, which develop hypertrophic cardiomyopathy with an increase in cardiac function [69], indicating that MEK1-ERK1/2 signaling induces a physiologic hypertrophy response associated with increased cardiac function and partial resistance to apoptosis [69]. In fact, while transgenic mice with activated MEK1 are resistant to ischemia–reperfusion injury, Erk2 +/- mice show an increase in infarction areas and apoptosis as compared to controls [70]. In addition, deletion of cardiac Erk1/2 in mice promotes stress-induced apoptosis and heart failure but has no effect on hypertrophy upon exercise stimulation or pressure overload [71].

In humans, few autosomal dominant genetic syndromes with mutations and constitutive activation in the Raf-MEK-ERK pathway are known (Leopard, Costello and Noonan syndromes). Affected patients develop hypertrophic cardiomyopathy, depicting again the central role of this pathway in cardiomyocyte proliferation and survival [72]. Following ischemia or stress, MEK1/2 and ERK1/2 have been shown to induce transduction of anti-apoptotic signals and thus to largely contribute to cardiomyocyte survival [66,73].

Given the pivotal role of MEK for cardiomyocyte maintenance and

survival in physiologic conditions and under stress, it is not surprising that the effects of MEKi on ventricular function are a consequence of specific blockade rather than a result of off-target effects. Possibly the inhibition of MEK1/2 is not sufficient to induce cardiotoxicity, and additional clinical and/or genetic co-factors such as hypertension or ischemia are required for phenotypic manifestation. This may explain the relatively low prevalence of severe adverse events under MEKi treatment.

Regarding hypertension, which remains the most common cardiovascular adverse event under BRAFi/MEKi, a complicated molecular loop involving overexpression of CD47 has been suggested as the underlying mechanism. In summary, compensatory ERK hyperactivation upon BRAF/MEK inhibition induces CD47 transcription which in turn inhibits nitric oxide stimulation, a pivotal regulator of the vascular tone and thus blood pressure [74,75].

Diagnostic work-up of suspected BRAFi/MEKi related cardiotoxicity

Insufficient data are currently available to provide evidence-based workup and follow-up guidelines for cardiac toxicities induced by BRAFi/MEKi. However, based on experience with other TKIs and evidence gathered from phase 2 and 3 studies with BRAFi/MEKi, recommendations can be formulated [18,76].

The first element to consider is the past medical history of the patients with particular attention to potential underlying cardiac conditions, irAEs from previous ICI therapy, and the presence of cardiovascular risk factors such as hypertension, age and obesity.

Before treatment initiation, as a baseline workup, we recommend to measure blood pressure, to perform an ECG for QTc interval documentation, a BNP/NT-proBNP dosage and a transthoracic echocardiography to assess the cardiac function. These elements will be crucial to grade potential adverse events that may occur during the treatment, to adapt the frequency of follow-up and for the objective decision of treatment discontinuation [77].

Early elevation of troponin I has been reported as a predictor of left ventricular dysfunction in patients receiving cytotoxic chemotherapeutic agents, but data on a similar association in patients treated with BRAF/MEKi is not available. BNP/NT-proBNP measurement may be useful to discriminate with a high negative predictive value patients with heart failure from those with non-cardiac causes for acute dyspnea during treatment [78]. In this perspective, a baseline measurement before BRAFi/MEKi treatment initiation might be useful, typically in patients with previous cardiac diseases. However, there is currently insufficient evidence to recommend the general use of a specific biomarker as a follow-up marker of BRAF/MEKi induced cardiotoxicity.

We recommend to abstain from treatment with MEKi and to consider alternatives in case of baseline QTc $>$ 500 ms and/or LVEF $<$ 40% and/or blood pressure $>$ 160/100 mmHg despite optimal treatment and in absence of a reversible cause such as ischemic cardiomyopathy. Indeed such a decision should be made in collaboration with the cardiologists who may propose further investigation or treatments of the above mentioned conditions, before considering the introduction of MEKi.

Most cardiovascular toxicities induced by MEKi are asymptomatic. Reports indicate early toxicities during the first month of treatment but also after 2 years [15,79]. Follow-up ECG for evaluation of QTc interval prolongation should be performed at 4 weeks of treatment initiation and subsequently every 3 months if normal. Blood pressure should be measured at every clinical visit. The cardiac follow-up strategy of patients under BRAFi/MEKi remains poorly defined and should ideally be based on pre-existing risk factors of cardiotoxicity as proposed by Lyon et al [77]. Thus, serial echocardiographic monitoring during treatment can be considered in patients with an intermediate or high baseline risk score before treatment initiation (e.g every 3 months) (Fig. 3). However, it is essential to emphasize that data supporting the use of a cardiac monitoring strategy over another are scarce. Furthermore, there is a crucial need to identify baseline risk factors and predictive biomarkers of developing BRAFi/MEKi induced cardiotoxicity. In case of moderately reduced LVEF (40–50%) at baseline, regular follow-up (initially every 2 weeks) with echocardiography, has been proposed [76]. Given the fact that late toxicities are also observed and the impracticability to repeat echocardiography every 2 weeks in the long term, the clinical evaluation plays a central role. Therefore, medical history should be taken with respect to ventricular dysfunction symptoms such as shortness of breath, edema, and chest pain. Careful examination of patients with focus on signs of heart failure should be performed at each clinical visit and guide decision to perform follow-up echocardiography (Fig. 3).

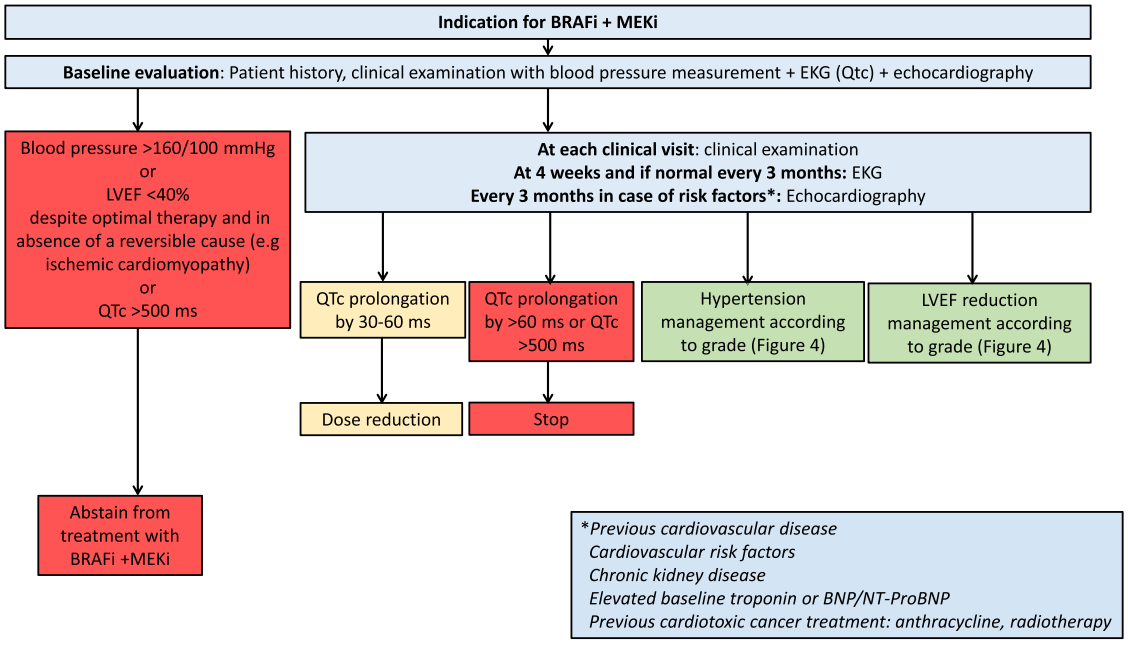

Fig. 3. Proposed algorithm for diagnostic workup of BRAFi/MEKi induced cardiotoxicity.

Management of BRAFi/MEKi induced toxicity

Although the natural history, prognosis and treatment of BRAiF/MEKi mediated cardiac events are not well established, several recommendations for management of toxicities can be made based on the currently available data.

If under treatment the QTc interval increases by>60 ms, or exceeds 500 ms, we recommend permanent discontinuation of therapy. In case of increase in QTc interval of 30–60 ms dose reduction should be performed.

In case of asymptomatic decrease in LVEF of < 10% (grade 1) or of 10–20% (grade 2) in comparison with baseline LVEF value to an absolute value below lower limits of the institutional normal value, MEK inhibitors should be interrupted for 4 weeks at least (BRAF inhibitors can be continued). If LVEF normalizes after therapy interruption, MEK inhibitor therapy may be resumed at a lower dose. Current evidence suggests that LVEF restores to baseline levels after treatment discontinuation [80]. In case of symptomatic decrease in LVEF or decrease > 20% (grade 3), or treatment refractory heart failure (grade 4), therapy should be permanently stopped, and symptomatic heart failure therapy prescribed under guidance of a specialized cardio-oncology unit.

In case of symptomatic decrease in LVEF or decrease > 20% (grade 3), or treatment refractory heart failure (grade 4), permanent treatment interruption should be considered, and heart failure therapy started and individualized under guidance of a specialized cardio-oncology unit. Although specific evidence of efficacy of established heart failure therapy in BRAFi/MEKi induced LV dysfunction is lacking, there is general evidence that neuro-hormonal modulation with drugs including angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARB) in association with betablockers provides cardiovascular benefit in case of reduced LVEF < 40% [81]. In patients with milder dysfunction (LVEF 40–50%), evidence is less robust but potential benefit may be expected with ARB and betablockers [82,83]. In all cases, symptomatic treatment with diuretics is warranted.

In case of grade 1 hypertension (>140/90 mmHg), therapy should be continued and anti-hypertensive drug initiated (e.g with ACE inhibitors or according to local practice). In case of blood pressure > 160/100 mmHg, or hypertension refractory to>1 anti-hypertensive drug (grade 2 hypertension), treatment should be discontinued until blood pressure normalization or reduction to grade 1 hypertension. Therapy should then be reintroduced at a lower dosage after the reduction of hypertension to stage 1 or below. In case of uncontrolled blood pressure, hypertensive crisis with organ lesions (grade 3 hypertension), treatment should be permanently stopped, and aggressive measures undertaken to control and normalize blood pressure (Fig. 4). Importantly, although vemurafenib, dabrafenib and cobimetinib are metabolized by the cytochrome P450 (CYP450) system and thus have significant potential for drug-drug interactions, no clinically relevant interactions with antihypertensive drugs are described or expected.

Except for severe life-threatening toxicities, decision of treatment discontinuation should not only be guided by the severity of the cardiac complication, but also integrate important oncologic considerations such as previous treatment lines and availability of effective treatment alternatives for a given patient.

Management of patients treated with both ICI and BRAFi/MEKi

Lately, the therapeutic arsenal of oncologists has been complemented with the option of simultaneously treating patients with different classes of anti-cancer drugs. Thus, triplet therapy, combining ICI and BRAFi/MEKi with the aim of affording the durability of immunotherapy response and the high response rate of targeted therapies, has been proposed and several trials exploring this strategy are still ongoing [84]. Whether the probability of developing cardiac side effects under triplet therapy is additive, with independent risks of developing drug class-specific events, or whether it is multiplicative remains to be determined. Furthermore, the impact of a sequential treatment strategy on the incidence and the range of possible cardiac side effects is also still poorly known. Despite the lack of data on the best cardiac side effects screening strategy under triplet therapy, we recommend a cautious approach with a clinical evaluation including blood pressure measurement, troponin dosage and EKG prior to each administration and to perform serial echocardiographic screening at least every 3 months [85].

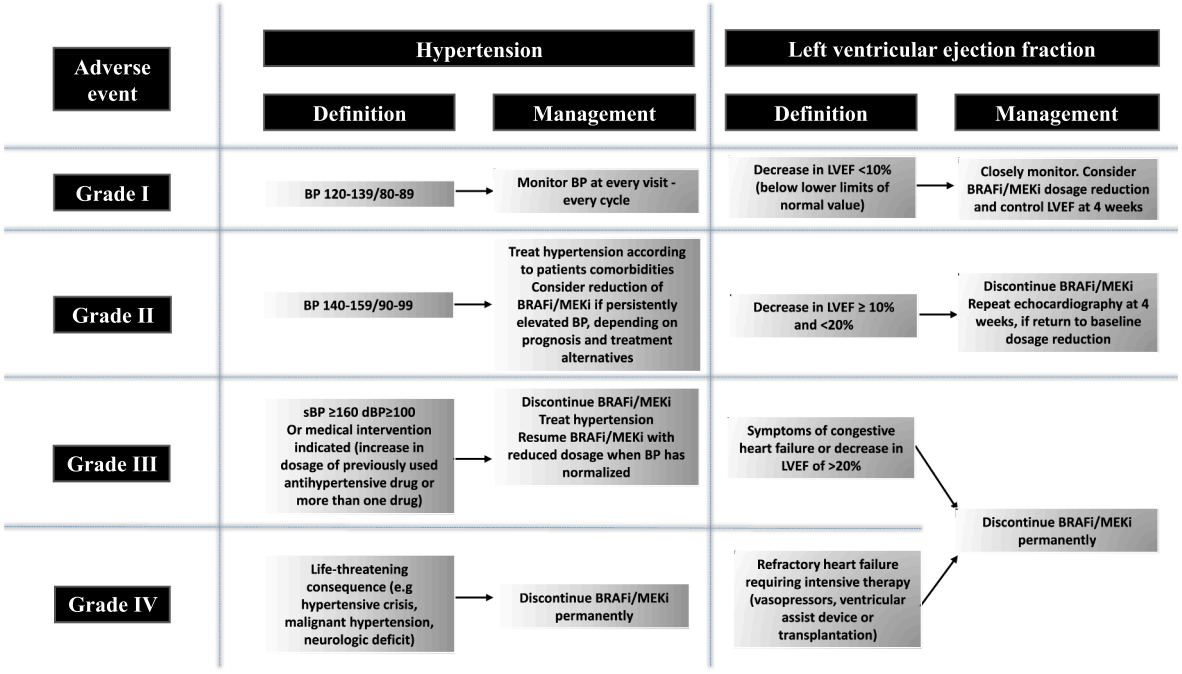

Fig. 4. Propositions for a grade dependent management of BRAFi/MEKi induced hypertension and left ventricular ejection fraction decrease.

Conclusions

Although ICI therapy was initially used to treat patients with melanoma or lung cancer, its indications are currently expanding to an increasing number of cancer types. Therefore, the incidence of cardiac irAEs will surely rise in the near future and not solely cardiologists and oncologists but all physicians implicated in the care of cancer patients must be aware of this important toxicity. ICI related cardiotoxicity currently remains a poorly understood entity. The presence of shared epitopes (e.g. troponin, desmin and myosin) between melanoma cells and myocardium is proposed as the main mechanism of ICI-induced myocarditis. An interdisciplinary approach is critical for accurate diagnosis and rapid initiation of therapy for this potentially lethal irAEs. Multicentric, prospective studies, aiming at identifying determinants of occurrence, prognostic biomarkers, and the best treatment strategy of cardiac irAEs are needed to improve patient management.

In contrast to ICI related cardiac irAEs, BRAFi/MEKi mediated cardiac adverse events are due to the important role of the Ras-Raf-MEK-ERK signaling in survival of cardiomyocytes. These cardiac effects are reversible upon treatment discontinuation or dose adaptation and symptomatic therapy is often sufficient to restore cardiac function.

A future important challenge will be to distinguish between ICI and BRAFi/MEKi induced cardiotoxicity in patients receiving triplet therapies.

Ethics approval and consent to participate

There is no ethics approval needed for this manuscript

Consent for publication

Not applicable

Availability of data and material

Not applicable

Funding

None

Authors' contributions: DA and ND wrote the manuscript and prepared the figures and table. OM and PM commented on and corrected the manuscript. BCÖ conceived the article, wrote the manuscript and prepared the figures and table. All authors read and approved the final manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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