Immuun checkpoint inhibitors (anti PD-1, anti PDL-1 en anti CTLA-4)

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Bijwerkingen

Bij behandeling met immuun checkpoint inhibitors kan cardiotoxiciteit optreden.

In het farmacotherapeutisch kompas[1] en ESMO guidelines[2] wordt cardiotoxiciteit bij immuuncheckpoint inhibitors gemeld als:

- hypertensie
- tachycardie
- aritmie (inclusief atriumfibrilleren)
- myocarditis
- pericardiale aandoeningen (pericarditis, pericardiale effusie, cardiale tamponade, Dressler-syndroom).
- vasculitis
- acuut coronair syndroom
- linker ventrikel disfunctie

Risico

Een verhoogd risico op cardio vasculaire toxiciteit ontstaat bij de volgende patiënten[3]:

- Combinatie immuuntherapie
- Andere immuungerelateerde bijwerkingen
- Eerder behandeld met cardiotoxische middelen (o.a. anthracyclines, herceptin, radiotherapie mediastinaal of thorax)
- > 75 jaar en/of patiënten die al bekend zijn met een ‘coronary artery disease’
- <10jr
- Auto-immuunziekte in de voorgeschiedenis
- (Ex)rokers
- Verhoogde cardiale enzymen voor start, diabetes mellitus, EF < 50%.

Ontstaan

Over het optreden van cardio vasculaire bijwerkingen bestaat nog veel onduidelijkheid. In het artikel van de ASCO[4] wordt vermeld dat deze bijwerkingen gemiddeld 1 tot 2 maanden na starten immuuntherapie optreden, maar dat deze in zeldzame gevallen tot een jaar na start kunnen ontstaan. In de ESMO Guideline[5] wordt een onderscheid gemaakt tussen inflammatoire (-itissen) en niet-inflammatoire immuungerelateerde cardiovasculaire toxiciteit. De inflammatoire bijwerkingen treden meestal op tijdens de eerste 4 kuren, maar een kwart treedt daarna op. Non-inflammatoire

[1] Zorginstituut Nederland (2023)
[2] Haanen et al. (2022)
[3] Lyon et al. (2022)
[4] Vuong & Yang (2023)
[5] Haanen et al. (2022)

bijwerkingen kunnen ontstaan na 3 maanden, maar in de meeste gevallen na 6 maanden. Aritmiën en atherosclerose kunnen gedurende de gehele behandeling optreden.

Cardiovasculaire complicaties ontstaan bij 5% van de patiënten die immuuntherapie krijgen. Een ernstige IR-myocarditis ontstaat in minder dan 1 % van de gevallen, maar heeft een geschat risico op overlijden van 25-50%. De lange termijn effecten van immuuntherapie op cardio vasculaire aandoeningen is nog onbekend. Recente studies geven aanwijzingen dat er een verhoogde kans is op het ontstaan van artherosclerose bij patiënten die behandeld zijn met immuuntherapie.

Symptomen

Klachten die kunnen duiden op cardiovasculaire bijwerkingen zijn: toenemende vermoeidheid, spierpijn of spierzwakte, hartkloppingen, pijn op de borst, flauwvallen, kortademigheid en perifeer oedeem. Ernstige gevallen kunnen zich uiten in een acute dood. Symptomen kunnen vaak gemaskeerd worden door bijkomende immuungerelateerde bijwerkingen (zoals myositis, pneumonitis, hypothyreoïdie) of klachten als gevolg van de kanker.
Immuungerelateerde vasculitis of -trombose kan pijnklachten, zwelling van de extremiteiten, vergrote zichtbaarheid van de vaten, purpurische rash, erytheem, pleurapijn, wheezing of hemoptoë veroorzaken.[6]

Behandeling

De behandeling van cardiovasculaire bijwerkingen bestaat volgens de ESMO Guideline[7] uit 3 onderdelen. Om te beginnen de behandeling van de cardiale complicaties volgens de cardiologische richtlijnen, bijv. het plaatsen van een pacemaker bij een blokkade. Tweede is immuunsupressie voor de myocarditis, pericarditis of vasculitis. De derde betreft de beslissing of de immuuntherapie (definitief) gestopt moet worden.

Onderzoeken bij verdenking op myocarditis, pericarditis, aritmieën, verminderde pompkracht met hartfalen en vasculitis: ECG, tropinine, CK (mb), BNP, echo van het hart, X-thorax.

[6] Schneider et al. (2021)
[7] Haanen et al. (2022)

TABLE 9. Cardiovascular Toxicities

9.1. Myocarditis, Pericarditis, Arrhythmias, Impaired Ventricular Function With Heart Failure, and Vasculitis

Workup and evaluation
- ECG
- Troponin, and CPK to rule out concurrent myositis, especially in patients treated with combination immune therapies. Alternative reasons for elevation should be ruled out.
- If elevated, troponin should be serially monitored. With elevated troponin, be aware of the potential for triple M irAEs—myositis, myasthenia, and myocarditis—and refer to subspecialties.
- BNP
- Echocardiogram
- Chest X-ray

Additional testing to be guided by cardiology and may include:
- Stress test
- Cardiac catheterization
- Cardiac MRI

Grading	Management
G1: Abnormal cardiac biomarker testing without symptoms and with no ECG abnormalities	All grades warrant workup and intervention, given the potential for cardiac compromise. Hold ICPi for G1 elevated troponin[a] and recheck troponin 6 hours later. May consider resuming once normalized or if believed not to be related to ICPi. Hold ICPi and discontinue for ≥ G2. For patients with grade ≥ 2, early (ie, within 24 hours) initiation of high-dose corticosteroids (1-2 mg/kg/d of prednisone, oral or IV depending on symptoms) should be considered as it is likely to be beneficial without adverse effects. Admit patient for cardiology consultation. Management of cardiac symptoms according to ACC/AHA guidelines and with guidance from cardiology. Immediate transfer to a coronary care unit should be considered for patients with elevated troponin or conduction abnormalities. For new conduction delay, consider a pacemaker. In patients without an immediate response to high-dose corticosteroids, consider early institution of cardiac transplant rejection doses of corticosteroids (methylprednisolone 1 g every day) and the addition of either mycophenolate, infliximab, or antithymocyte globulin.[210] Consider abatacept (costimulatory molecule blockade) or alemtuzumab (CD52 blockade) as additional immunosuppression in life-threatening cases.[211,212]
G2: Abnormal cardiac biomarker testing with mild symptoms or new ECG abnormalities without conduction delay	
G3: Abnormal cardiac biomarker testing with either moderate symptoms or new conduction delay	
G4: Moderate to severe decompensation, IV medication or intervention required, life-threatening conditions	

Qualifying statement: Treatment recommendations are based on anecdotal evidence and the life-threatening nature of cardiovascular complications. Holding checkpoint inhibitor therapy is recommended for all grades of complications. The appropriateness of rechallenging remains unknown. Note that infliximab has been associated with heart failure and is contraindicated at high doses (ie, > 5 mg/kg) in patients with moderate-severe heart failure.[213,214]

9.2 Venous Thromboembolism

Workup and evaluation
- Evaluation of signs and symptoms of PE or DVT may include:
  - Clinical prediction rule to stratify patients with suspected VTE
  - Venous ultrasound for suspected DVT
  - CTPA for suspected PE
  - Can also consider D-dimer for low-risk patients based on risk stratification by clinical prediction rule for DVT/PE when CT or Doppler not available or appropriate
  - V/Q scan is also an option when CTPA is not appropriate
  - Consider other testing, including ECG, chest radiography, BNP and troponin levels, and ABG

Grading	Management
G1: Venous thrombosis (eg, superficial thrombosis)	Continue ICPi. Warm compress. Clinical surveillance.

(continued on following page)

TABLE 9. Cardiovascular Toxicities (continued)

9.2 Venous Thromboembolism

G2: Venous thrombosis (eg, uncomplicated deep vein thrombosis), medical intervention indicated	Continue ICPi. Management according to CHEST, ACC, and/or AHA guidelines and consider consult from cardiology or other relevant specialties. LMWH, VKA, dabigatran, rivaroxaban, apixaban, or edoxaban for initial anticoagulation treatment. For long-term anticoagulation, LMWH, edoxaban, rivaroxaban, or apixaban for at least 6 months are preferred over VKAs because of improved efficacy.[215,216] IV heparin is an acceptable alternative for initial use and oral anticoagulants are acceptable for the long term.
G3: Venous thrombosis (eg, uncomplicated PE), urgent medical intervention indicated	Hold ICPi and may reintroduce after risk and benefit are considered. Follow G2 anticoagulation recommendations.
G4: Life-threatening consequences; hemodynamic or neurologic instability; organ damage; loss of extremity(ies)	Hold ICPi and may reintroduce after risk and benefit are considered. Admit patient and management according to CHEST, ACC, and/or AHA guidelines and with guidance from cardiology. Respiratory and hemodynamic support. Follow G2 anticoagulation recommendations with further clinical management as indicated based on symptoms.

Additional considerations

- VTE prophylaxis in high-risk outpatients with cancer (Khorana score of 2 or higher before starting a new systemic regimen) may be offered thromboprophylaxis with apixaban, rivaroxaban, or LMWH, provided there are no significant risk factors for bleeding and no drug interactions, as per ASCO VTE guideline.[215]
- Although it may be impossible to determine the etiology of thromboembolic disease in patients with advanced cancer and the role, if any, that ICPi treatment plays, it is reasonable to remove the potential inciting agents, given the severity and life-threatening potential of grade 4 complications. Clinicians are to use clinical judgment and take into account the risks and benefits when deciding whether to discontinue ICPi treatment.
- Anticoagulant therapy duration should continue while on immunotherapy and consideration be given to continuing for an additional 6 months following completion of immunotherapy.[215]

Abbreviations: ABG, arterial blood gas; ACC, American College of Cardiology; AHA, American Heart Association; BNP, brain natriuretic peptide; CHEST, American College of Chest Physicians; CPK, creatine phosphokinase; CT, computed tomography; CTCAE, Common Terminology Criteria for Adverse Events; CTPA, computed tomography pulmonary angiography; DVT, deep vein thrombosis; ICPi, immune checkpoint inhibitor; irAE, immune-related adverse event; IV, intravenous; LMWH, low-molecular-weight heparin; MRI, magnetic resonance imaging; PE, pulmonary embolism; US, ultrasound; VKA, vitamin K agonist; VTE, venous thromboembolism.

[a]According to CTCAE v5.0, G1 elevated troponin is defined as levels above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer.

Specifiek voor behandeling van IR myocarditis zie onderstaand schema

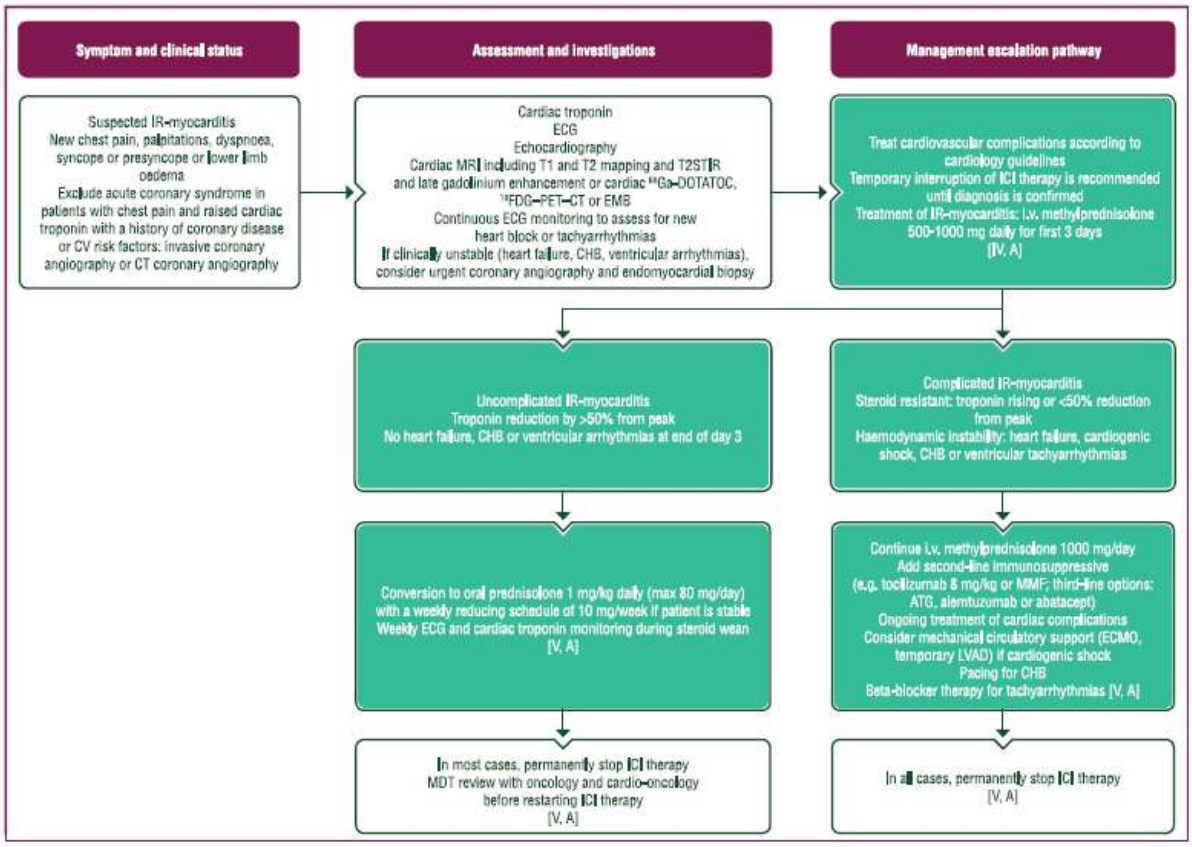


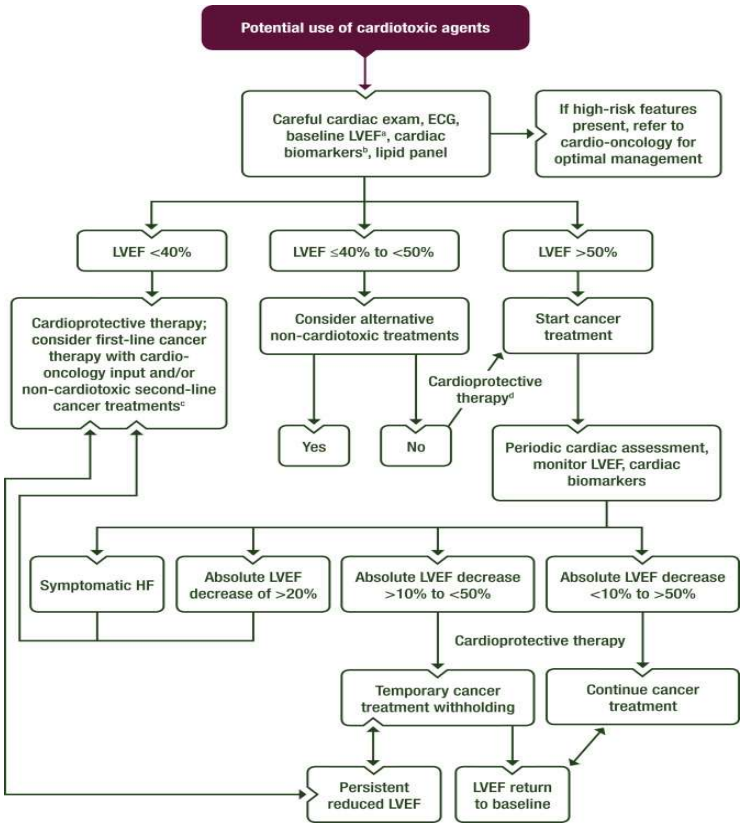
Figure 9. Management of IR-myocarditis.
Purple: general categories or stratification; turquoise: combination of treatments or other systemic treatments; white: other aspects of management.
^{18}FDG, [^{18}F]2-fluoro-2-deoxy-D-glucose; ^{68}Ga-DOTATOC, Gallium-68-DOTA(0)-Phe(1)-Tyr(3)-octreotide; ATG, anti-thymocyte globulin; CHB, complete heart block; CT, computed tomography; CV, cardiovascular; ECG, electrocardiogram; ECMO extracorporeal membrane oxygenation; EMB, endomyocardial biopsy; ICI, immune checkpoint inhibitor; IR, immune-related; i.v., intravenous; LVAD, left ventricular assist device; MDT, multidisciplinary team; MMF, mycophenolate mofetil; MRI, magnetic resonance imaging; PET, positron emission tomography; T2STIR, T2-weighted short tau inversion recovery.

(Haanen et al., 2022)

Screening

Bij elke patiënt die een oncologische systemische behandeling ondergaan, moet een risicoprofiel bepaald worden. Patiënten met (een verhoogd risico op) cardiovasculaire aandoeningen vooraf aan de behandeling, hebben een relatief hoger risico op cardiovasculaire bijwerkingen tijdens de behandeling.

Voor inschatten risicoprofiel kan onderstaand stroomschema gehanteerd worden:



(Curigliano et al., 2020)

Bij patienten met een laag risico wordt geadviseerd om voor start van de behandelingen een ECG te doen en troponine T en NT-proBNP te bepalen in het lab.

Bij patiënten met een verhoogd risico wordt tevens een echo van het hart geadviseerd.

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