Cardiotoxicity associated with immunotherapy

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Cardiac complications secondary to immunotherapy are rare because they represent less than 1%. However, they are associated with the highest mortality, around 40%. They have been described with all currently approved agents, although we have scarce data and only from case reports or small case series. According to a review of the pharmaceutical safety databases, cardiac complications had an incidence of 0.1%, although this number is probably underestimated due to the absence of systematic monitoring in trials of this type of complications. On the other hand, it is foreseeable that the incidence will increase since the use of immunotherapy is spreading to many types of tumors and, therefore, more patients will be susceptible to be treated with them in the future.

What has been clearly seen is that the risk increases considerably when combination therapy is used (anti-CTLA-4 antibodies with anti PD1 or anti PDL1 antibodies). For example, in patients undergoing combination therapy with Ipilipumab (antiCTLA4) and Nivolumab (anti PD1), the incidence of complications was 0.27% compared to 0.06% in patients who underwent treatment with Nivolumab alone.

These complications usually appear early, with a median onset of 10 weeks after starting treatment, although they may appear from 2 weeks after its initiation and up to 17 weeks after the end of the treatment. Multiple cardiac complications have been described including myocarditis, pericarditis, pericardial effusion, arrhythmias, conduction abnormalities, arterial hypertension, cardiomyopathy, ventricular dysfunction, “Tako-Tsubo” syndrome and even acute coronary syndrome. It has been shown that both innate and adaptive immunity promote the development of plaques of atheroma, their progression and destabilization. The presentation can be variable, but we have to think about them if the patient reports chest pain, dyspnea, peripheral edema or palpitations. Diagnosis can be difficult, on the one hand because sometimes patients refer nonspecific symptoms and on the other hand because these symptoms may be due to disease’s progression, to other complications such as pulmonary thromboembolism or other complications derived from immunotherapy, such as pneumonitis. Mortality is high, with death frequently secondary to refractory arrhythmia or cardiogenic shock.

Immune myocarditis is one of the most commonly described cardiac complications in the literature because it can be fulminating, progressive and life-threatening. It may result in heart failure or arrhythmia. It can present itself associated with myositis, and

also with myasthenia gravis in some cases. It is more common with combination therapy, although up to 66% of cases can occur with single therapy. In addition, we must take into account that up to 51% of patients may have a normal LVEF, a difference compared with other causes of myocarditis. The mechanism is explained on the one hand possibly due to cross-reactivity against common antigens and on the other hand because there are preclinical data that suggest that both CTLA-4 and PD-1 play critical roles regulating immune homeostasis in the myocardium.

Regarding diagnosis, although there is no evidence of what is the best monitoring strategy to follow, it seems reasonable to try to establish a baseline cardiovascular risk through a detailed clinical history (cardiovascular risk factors, previous cardiological history, history of myocarditis, previous use of other cardiotoxic drugs...) and perform an ECG and cardiac biomarkers prior to the start of immunotherapy, especially taking into account the potential severity of cardiological complications. In high cardiovascular risk patients or in those with an established cardiac disease, a cardiological assessment would be advisable. Some groups recommend cardiac monitoring especially in the first weeks of treatment, with a new ECG and new biomarkers. Once treatment is started, if a cardiac complication is suspected, a new ECG, biomarkers and chest x-ray should be performed to rule out other etiologies that may justify the patient's symptoms, both cardiological, like acute coronary syndrome (using cardiac stress testing, heart catheterization or cardiac MRI) or other possible causes (thromboembolism, pneumonitis, disease's progression). It would be advisable to perform continuous cardiac monitoring and refer to a cardiologist to complete the study using echocardiography, cardiac MRI (especially if we suspect myocarditis, since it would be the preferred non-invasive technique for diagnosis) and endomyocardial biopsy for patients who are unstable or fail to respond to initial therapy or in whom the diagnosis is in doubt.

Holding checkpoint inhibitor therapy is recommended for all grades of cardiac complications, including grade 1 (asymptomatic biomarker elevations), and reinitiating therapy is almost never recommended. Treatment for mild-moderate complications (grades 2-3) consists of systemic corticosteroids at doses of 1 or even 2 mg / kg per day. In patients with no response after 3-5 days or in patients with severe toxicity (including moderate to severe decompensation, highly abnormal testing, fulminant disease, cardiogenic shock, acute heart failure or with life-threatening arrhythmia), higher doses of corticosteroids are needed and an additional immunosuppressive therapy should be added, such as tacrolimus, mycophenolate mofetil or thymoglobulin. It is not recommended to add infliximab as it has been associated with heart failure and its use is contraindicated in doses higher than 5 mg / kg in patients with advanced heart failure (Class III / IV). In cases in which myocarditis is suspected, some groups recommend systemic corticosteroids at doses of 1 g per day for 3 days followed by 1 mg / kg / day, evaluating adding other immunosuppressants agents if there is no adequate response. Contraction and conduction disturbances may improve after holding immunotherapy and with appropriate treatment. The patient's disease status must be taken into account before excessive support measures are performed. There are no recommendations on the resumption of immunotherapy, although it seems reasonable not to restart it, especially in patients who have presented with immune myocarditis.

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