Statins and Chemotherapy-induced Cardiotoxicity

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Chemotherapy-induced cardiotoxicity (CIC) is a heterogenous term that describes cardiotoxic effects from cancer therapeutics and encompasses mild asymptomatic myocardial injury and symptomatic heart failure with a decline in left ventricular ejection fraction (LVEF). The term chemotherapy-induced cardiotoxicity is often interchangeably used with chemotherapy-induced cardiomyopathy. Some individual studies have suggested that statins may also play an important role in decreasing the risk of CIC. A significant reduction in the incidence of chemotherapy-induced cardiomyopathy and the degree of LVEF decline in patients in the statin group compared to those in the control group.

Keywords: statin ; cardiotoxicity ; heart failure ; cardio-oncology

1. Introduction

Cancer is one of the leading causes of mortality worldwide, with 9.9 million cancer-related deaths reported in 2020 [1][2][3][4]. Successful cancer treatments are on the rise, and so cancer survivorship continues to increase. Although chemotherapy has remained as one of the essential cancer treatment measures, various adverse effects have been noted, including chemotherapy-induced cardiotoxicity (CIC), which is characterized by a progressive decline in the left ventricular ejection fraction (LVEF) and subsequent heart failure, either in a reversible, stress-induced fashion [5][6][7] or in an irreversible manner that can be fatal and/or chronic [8][9][10].

The incidence of CIC is estimated to be around 1–5% of all cancer patients, and it typically occurs in a dose-dependent fashion [11][12][13]. In particular, patients receiving anthracyclines such as doxorubicin and HER2/neu receptor monoclonal antibodies including trastuzumab are more at risk of developing CIC [14]. Importantly, patients who develop CIC have been shown to have up to 3.5 times higher risk of mortality than those with cardiomyopathy from other causes. It may be because those with CIC often have sub-clinical disease progression in the early stages, with overt changes in symptoms only after they have sustained a significant level of cardiac damage [13], and limited preventive and treatment options are available, such as beta-blockers, angiotensin-converting enzyme inhibitors (ACEIs), and angiotensin receptor blockers (ARBs) [15][16].

2. Statin Use Can Attenuateand Chemotherapy-induced cardiotoxicity

Statins may provide a significant preventive benefit against CIC, especially for those who received anthracyclines and trastuzumab. We found that patients in the control group who did not receive statins with chemotherapy had a more significant decline in LVEF compared to those of the statin group (WMD = −6.08%, 95% CI: −8.55 to −3.61, $p < 0.001$). In addition, those who received concurrent statins in the statin group had lower odds of developing CIC compared to the control group (OR = 0.41, 95% CI = 0.28–0.60, $p < 0.001$). These results suggest that statins are promising cardioprotective agents against CIC.

Interestingly, those who received statins were more likely to have cardiovascular risk factors, including diabetes mellitus, hypertension, or coronary artery disease, as reported by Carvillo-Argüelles et al., Chotenimitkhun et al., and Seicean et al. Nevertheless, the authors found that statin use was independently associated with a reduced occurrence of CIC after adjustment for these risk factors. In addition, Abdel-Qadir et al. demonstrated that those who received statins had a lower risk of CIC in their sensitivity analyses, removing those who had interim acute myocardial infarction with imputation of the elevated low-density lipoprotein levels. The results suggested that the protective mechanism of statins may be independent of their cholesterol-lowering effects. Although the exact pathophysiology of CIC remains unclear, it is proposed that drugs such as anthracyclines increase the production of oxygen-derived free radicals in cardiac myocytes and increase the intracellular anthracycline-iron complex accumulation [14][17][18][19][20], leading to increased oxidative stress and subsequent necrosis of the cells. Statins, or hydroxymethylglutaryl-CoA (HMG-CoA) reductase inhibitors, which

are cholesterol-lowering drugs primarily used for primary and secondary prevention of cardiovascular diseases, have also been shown to render prophylactic effects against CIC via their action of reducing oxidative stress at the cellular level [21][22].

Although cardiac dysfunction related to chemotherapy could be addressed with an interruption or discontinuation of chemotherapy, the cessation of chemotherapy in cancer patients may be related to poor clinical outcomes from the oncology standpoint. Furthermore, 0.5–2.5% of patients with chemotherapy-induced cardiomyopathy may have end-stage heart failure requiring a left-ventricular assist device or even heart transplant [9][10][23][24][25]. Due to the possible poor trajectory, guidelines for prevention and surveillance of chemotherapy-induced cardiomyopathy are imperative. Several trials assessing the efficacy of statins in preventing CIC are underway, including a trial investigating the effect of atorvastatin in the preservation of LVEF 24 months after initiation of anthracycline-based adjuvant therapy for breast cancer patients in the National Institutes of Health (NIH) sponsored study PREVENT (Preventing Anthracycline Cardiovascular Toxicity with Statins) [26].

The study presents promising evidence that statins may provide significant cardioprotective effects for those receiving cardiotoxic chemotherapy, and further investigation into the role of statins against CIC is important in this regard.

3. Conclusions

In conclusion, via meta-analysis, statins were found to have a cardioprotective effect against chemotherapy-induced cardiomyopathy. Specifically, the control group, which did not receive statins, had a more significant decline in LVEF after chemotherapy, with a WMD of −6.08% (95% CI: −8.55–−3.61, $p < 0.001$), compared to the statin group. Additionally, compared to the control group, the statin group had a significantly lower incidence of chemotherapy-induced cardiomyopathy (OR = 0.41, 95% CI = 0.28–0.60, $p < 0.001$). Further, a larger-scale RCT with extended follow-up period is needed.

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