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Editorial

Statins in Cardio-oncology: Holy Grail or Epiphenomenon

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See article by Calvillo-Argüelles et al., pages 153–159 of this issue.

The introduction of trastuzumab, a monoclonal antibody against the human epidermal growth factor receptor-2 (HER2), revolutionized therapy for patients with HER2+ breast cancer. This subset of tumors, accounting for approximately 20% of breast cancers, was associated with more aggressive behaviour and inferior survival. In landmark oncology trials, the addition of trastuzumab to standard adjuvant chemotherapy reduced the incidence of disease recurrence by 50% and improved survival by 33%.[1] As the real-world experience with trastuzumab grew, it became apparent that this agent was also associated with a significant risk of developing clinical and subclinical left ventricular (LV) dysfunction, particularly when used in combination with anthracycline chemotherapy. In observational studies, the risk of asymptomatic LV dysfunction in patients receiving adjuvant trastuzumab is reported to be as high as 20%.[2]

Traditionally, recommended management of trastuzumab cardiotoxicity has involved drug withdrawal until recovery of LV function is observed; use of LV enhancement therapies in this setting is recommended,[3] but is at the discretion of treating physicians and clinical practice may vary widely. A major limitation of this approach is that it calls for treatment interruption and resultant worse cancer outcomes,[4] as well as LV dysfunction that may be irreversible. As such, much interest has been focused on the use of cardioprotective therapies to prevent LV dysfunction in the first place. Most randomized studies of cardiotoxicity prophylaxis have focused on anthracycline-treated populations, but many patients in these studies also received trastuzumab. In this context, statistically significant but sometimes clinically questionable benefits have been demonstrated for β-blockers and renin-angiotensin-aldosterone system inhibitors. A randomized trial of cardioprotection in a HER2+ cohort showed that perindopril and bisoprolol prevented cardiotoxicity in patients receiving trastuzumab, with or without prior anthracycline treatment.[5] The absolute difference in final LV ejection fraction (LVEF) between treatment and placebo groups, however, was only 3% for perindopril and 5% for bisoprolol. Because patients with cancer are often intolerant of the antihypertensive and biochemical side effects of β-blockers and renin-angiotensin-aldosterone system inhibitors,[6] the search has continued for a cardioprotective strategy that is both more efficacious and better tolerated than what is currently available.

Statins are an appealing option for a number of reasons. The anti-inflammatory effect of these agents and their ability to reduce oxidative stress and free radical generation are compatible with our understanding of cancer therapy–related cardiotoxicity, particularly due to anthracyclines.[7] Furthermore, statins are generally better tolerated than typical LV enhancement therapies. Finally, because of the overlap of risk factors between cardiovascular disease and cancer, traditional atherosclerotic risk factors such as diabetes, dyslipidemia, and coronary artery disease may be more prevalent in patients with breast cancer than in the general population.[8] Therefore, a sizable proportion of these patients may have indications for statin therapy independent of cardiotoxicity risk. Earlier observational studies of statins in anthracycline-treated patients demonstrated significant reductions in heart failure (HF) hospitalization[7] and decline in LVEF,[9] thereby supporting their potential role in attenuating the risk of developing cardiotoxicity.

In this issue of the *Canadian Journal of Cardiology*, Calvillo-Argüelles and colleagues[10] have expanded the existing body of knowledge on statins in anthracycline-treated patients[9] by examining the cardioprotective effects of these agents among patients with breast cancer who are treated with trastuzumab.[10] By using age- and treatment-matched controls, they identified a statistically significant benefit of statins in this patient population that persisted after adjustment for confounders. In patients receiving a median of 17 cycles of trastuzumab, the final LVEF after a median of 11 months of follow-up was 61.1% in the control group and 64.4% in the statin group ($P = 0.026$). The incidence of cardiotoxicity was numerically higher in the control group (24.4% vs 11.6%) based on a commonly accepted definition for cardiotoxicity. After adjustment for cardiac risk factors, statins were associated with a statistically significant 68%

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reduction in the risk of cardiotoxicity. Perhaps more important, trastuzumab interruption occurred half as often in statin-treated patients. Because interruptions in trastuzumab may be associated with inferior cancer outcomes, this is an important end point in itself. A therapy that can prevent LV dysfunction while simultaneously optimizing delivery of cancer treatment is a true "win-win" in cardio-oncology.

It is important to keep the magnitude of effect in perspective: The difference in final LVEF between groups was only 3.3%; looked at another way, there was no change in LVEF among statin-treated patients, whereas control patients experienced a median deterioration in LVEF of 6% over the study period. These changes are small but consistent with the trastuzumab-associated LVEF changes seen in a number of recent randomized studies.[5,11] At the same time, although the median change in LVEF was only 6%, 24% of patients in the control group experienced a clinically significant decline in LVEF, based on our current definitions. Assuming that there is a genuine signal of cardioprotection with statins, our challenge should be to identify those patients who are most likely to benefit. As with β-blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers, it is not practical from a system or patient perspective to routinely use a cardioprotective strategy that will ultimately only benefit a few.[6]

Based on its observational design, the results of this study can only be described as hypothesis generating. A number of important limitations, common to all observational studies, affect the interpretation of the results. If the findings of this and earlier observational studies in anthracycline-treated patients are real, and not due to confounding or other sources of bias, statins would appear to be a cardio-oncology panacea, offering protection against breast cancer treatment—related LV dysfunction by means of a well-tolerated and easily administered drug. The crucial question, then, is whether the observed effect is real? A few key findings suggest caution is warranted before wholeheartedly embracing statins as the cure-all in cancer therapy—associated LV dysfunction.

In the study by Calvillo-Argüelles and colleagues,[10] the benefit of statins was seen among the 56% of patients who had previously received anthracyclines, but also in those who had not. We now have observational evidence supporting a protective effect of statins in patients receiving anthracyclines alone, trastuzumab alone, and sequential combination therapy. By contrast, statins have had only modest effects in preventing HF across randomized primary and secondary prevention trials outside the cardio-oncology literature,[12] and they have no benefit in patients with established HF.[13] The mechanisms by which anthracyclines and trastuzumab cause toxicity are completely distinct. Although the benefits of statins are pleiotropic and extend beyond lipid lowering, one must wonder why such a pronounced effect of statins would be seen in breast cancer therapy—associated LV dysfunction, but not when other causes of cardiomyopathy and HF are considered.

Perhaps the most remarkable finding of this article and of earlier work in anthracycline-treated patients is that statin-treated patients experienced less cardiotoxicity than controls, despite a higher baseline cardiovascular risk. Patients in the statin group of the present study were more likely to be diabetic (37% vs 5%), hypertensive (58% vs 22%), and dyslipidemic (100% vs 11%), and more likely to have a history of established coronary artery disease (12% vs 2%). This may reflect a protective effect of statins that mitigates even the excess baseline risk of treated patients compared with controls. On the other hand, it is also possible that statin prescription was simply a surrogate marker for having received appropriate risk factor screening and preventive care. Perhaps a larger proportion of patients in the control group had undiagnosed diabetes, dyslipidemia, or hypertension, contributing to unmeasured confounding. This may introduce significant bias that can only be overcome with a prospective and ideally randomized trial.

Cardio-oncology, now 22 years old, remains a nascent specialty. As specialized clinics develop in academic centres, and as national and international networks bring these clinics together in collaboration, we should expect more prospective multicenter studies examining questions such as the one posed by these authors. Calvillo-Argüelles and colleagues[10] have performed a well-executed retrospective study of statins in patients receiving trastuzumab and have made every available effort to overcome the potential bias and confounding that are inherent in this type of study design. Their article is hypothesis generating and substrate for a randomized trial of statins as cardioprotection in this population. If their findings are confirmed in a prospective trial, they will have made an important step in the journey toward optimizing cancer outcomes without sacrificing long-term cardiac morbidity and mortality.

Disclosures

The authors have no conflicts of interest to disclose.

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