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EDITORIAL COMMENT

Post-Transplantation Cyclophosphamide

An Old Nemesis to a New Transplant Paradigm?*

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High-dose cyclophosphamide (Cy) has long been recognized as the cause of serious, potentially fatal, cardiac complications with hematopoietic cell transplantation (HCT). High-dose Cy as part of the preparative regimen for HCT was first pioneered in the 1970s, and it was soon evident that high doses (>120 to 200 mg/kg) could cause severe acute cardiomyopathy (1). The clinical syndrome was associated with diffuse voltage loss on electrocardiography, cardiomegaly, pulmonary vascular congestion, pleural and pericardial effusions, and decreased fractional shortening and increased end-diastolic volume. Postmortem examination revealed hemorrhagic myocardial necrosis, left ventricular wall thickening, and fibrinous pericarditis (2). Although several risk factors have been proposed, acute Cy cardiotoxicity seems to be most correlated with dose (3). Although some degree of dose-dependent cardiotoxicity remains evident with lower cumulative dosing of Cy (4), the acute left ventricular systolic dysfunction (LVSD) and myocardial necrosis from Cy is now relatively rare.

Allogeneic HCT traditionally uses human leukocyte antigen (HLA)-matched donors, either from a full sibling or matched unrelated donor. Historically, high-dose Cy, with cumulative doses of 120 to 200 mg/kg divided over 2 to 4 days, has been used as part of the pre-HCT conditioning regimen to provide potent immunosuppression and ablation of the recipient bone marrow, allowing for engraftment of donor cells. Currently, in the post-HCT setting, the additional use of high-dose Cy, most commonly dosed at 100 mg/kg divided over 2 days (day +3 and +4), has now allowed for successful transplantation with HLA-mismatched haploidentical donors (5). Post-transplantation Cy (PT-Cy) is thought to induce peripheral tolerance by suppressing alloreactive T cells, thus mitigating the complication of severe graft-versus-host disease (GVHD) typically expected in mismatched HCT. This has expanded access to HCT for many patients without a suitable donor, as nearly all HCT recipients have a potential familial haplo-donor (e.g., parent, child, sibling). PT-Cy has been so effective as a GVHD prevention strategy that its use has further expanded to HLA-matched donors (6). Altogether, the use of Cy, in both the pre-HCT conditioning and post-HCT setting, thus continues to increase considerably, making our understanding of Cy cardiotoxicity critically important.

In this issue of *JACC: CardioOncology,* Duléry et al. (7) provide important data on the association of early cardiac events (ECEs) and PT-Cy. The authors performed a detailed retrospective study comparing ECEs in patients receiving PT-Cy versus no PT-Cy. ECEs were defined as LVSD, acute pulmonary edema, arrhythmia, pericarditis, or acute coronary syndrome occurring within 3 months after HCT. The authors report increased ECEs in the PT-Cy group (19% PT-Cy vs. 6% no PT-Cy; $p < 0.001$). Although there were no differences in survival outcomes between the PT-Cy and no PT-Cy groups, ECE was associated with significantly worse survival (hazard ratio: 2.7; $p < 0.0001$). There are a scarcity of studies evaluating the cardiovascular (CV) effects of high-dose Cy in the modern era, and this paper is the first that we are aware of that specifically compares

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cardiac events in patients receiving PT-Cy versus no PT-Cy in a contemporary cohort. Additional strengths include uniform data on post-HCT echocardiography for all patients, as well as data on several conventional and treatment-related CV risk factors as potential confounders.

However, there are limitations. One of the challenges of studying CV effects in HCT is attributing causality, given the multitude of confounding events. HCT, particularly with haploidentical transplantation and PT-Cy, can be associated with complications from cytokine release syndrome, delayed immune reconstitution and increased infection/sepsis, which may all contribute to LVSD (5). In fact, in other studies of PT-Cy, a direct relationship between PT-Cy and cardiomyopathy has not been demonstrated. Rather, cardiac events occurred primarily in the setting of infectious complications (8). Furthermore, the contribution of large-volume fluids mandated by high-dose Cy regimens, concomitant renal insufficiency, hypoalbuminemia, and electrolyte disturbances are all important factors to take into account when considering the results of this study.

Acute LVSD from Cy is hypothesized to be due to direct endothelial damage by the drug itself and free radical injury by its metabolites, which induces additional endothelial and myocyte injury leading to extravasation of toxic metabolites and proteins. Microthrombosis further leads to ischemic damage, which may be responsible for the more lethal cardiotoxicity (2). The role of these mechanisms in the ECEs reported by Duléry et al. (7) and the contribution of Cy to late CV complications remain unclear. Although they report normalization of left ventricular ejection fraction in 14 of 23 patients, wall motion abnormalities persisted in the majority, and none had complete normalization of their echocardiograms at 3 months. Furthermore, ECEs had a detrimental impact on survival, suggesting important long-term impact.

There is an important need to define predictors of cardiotoxicity in patients receiving PT-Cy. A number of risk factors for CV events after transplantation have been previously described, including demographic (age, sex) and conventional CV- (obesity, hypertension, diabetes, dyslipidemia) and cancer-related factors (anthracycline, radiation exposure) (9). Duléry et al. (7) did not find that any association of traditional CV risk factors, anthracyclines, or radiation with ECEs, suggesting that other factors may be more predictive of post-transplantation CV disease. Accordingly, it is not clear if additional or more intensive pre-HCT CV assessments are likely to reduce potential PT-Cy cardiotoxicity.

The precise contribution of HCT therapeutic exposures on short- and long-term cardiac dysfunction thus remains to be further defined; and additional questions remain.

What is the role of pharmacokinetics and genetic predisposition? It is unclear whether genetic polymorphisms may also play a role with Cy. Direct toxic effects of Cy appear to be mediated by drug pharmacokinetics (10), but studies evaluating the differences in Cy pharmacogenetics, particularly in the transplantation setting, are limited.

Can biomarkers or imaging guide us to detect changes in cardiac function and predict subsequent events? Several biomarkers have been investigated in their roles in both CV disease and cancer, and they represent an opportunity to better risk stratify and diagnose patients. However, studies evaluating biomarkers to predict cardiotoxicity in HCT have been varied. Individual variability, thresholds of significance, and, ultimately, identification of an ideal biomarker remain elusive. Serial imaging via echocardiography and other modalities to detect early changes also represent a potential opportunity to better monitor or predict cardiotoxicity. However, like biomarkers, several questions remain, including thresholds for intervention, optimal screening intervals, and cost-effectiveness.

Is there a role for cardioprotective agents? Several neurohormonal therapies have been investigated to reduce the risk of CV disease in cancer patients (11). The potential of these pharmacologic strategies to prevent or ameliorate Cy-related cardiac events remains unknown.

What is the impact on pediatric populations? Although older adults appear to be at increased risk for ECE after HCT, Cy cardiotoxicity is not limited to adults. Early studies of Cy also demonstrated hemorrhagic pericarditis in children, and more recent studies have also shown a relationship between Cy and LVSD in pediatric populations (12). The detrimental impact of late CV effects in pediatric cancer survivors is substantial, and the inclusion of this population in further investigations is needed.

With the increasing use of PTCy, the data remain limited on the relative contribution of Cy to both early and late cardiotoxicity. Overall, this study demonstrates an important association of PT-Cy with ECEs and subsequent worse outcomes. The intersection between CV disease and cancer/cancer therapy is increasingly recognized. Additional studies defining pathogenesis, risk factors, biomarkers, and potential preventive therapy, particularly in the HCT setting, are critically needed.

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