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Treatment of Dyslipidemia in Allogeneic Hematopoietic Stem Cell Transplant Patients

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As survival rates in allogeneic hematopoietic stem cell transplantation (HSCT) continue to improve, attention to long-term complications, including cardiovascular disease, becomes a major concern. Cardiovascular disease and dyslipidemia are a common, yet often overlooked occurrence post-HSCT that results in significant morbidity and mortality. Also, increasing evidence shows that several anti-hyperlipidemia medications, the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors in particular, may have a role in modulating graft-versus-host disease (GVHD). However, factors such as drug–drug interactions, adverse effect profiles, and the relative efficacy in lowering cholesterol and triglyceride levels must be taken into account when choosing safe and effective lipid-lowering therapy in this setting. This review seeks to provide guidance to the clinician in the management of dyslipidemia in the allogeneic HSCT population, taking into account the recently published American College of Cardiology/American Heart Association guidelines on hyperlipidemia management, special considerations in this challenging population, and the evidence for each agent's potential role in modulating GVHD.

INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (HSCT) represents a potentially curative therapy for a number of life-threatening conditions. Because of advances in patient care, survival outcomes in allogeneic HSCT have improved substantially over the years [1-3]. The National Marrow Donor Program analysis reported that 1-year survival rates for patients receiving a transplant from an unrelated donor have increased from 42.2% from 1996 to 2001 to 61.8% in the most recent 2008-2010 dataset [4]. Survival for unrelated donor transplants has even been shown to be comparable with related donor transplants in certain populations [5-7]. With continued improvements in HLA matching, supportive care measures, and control of graft-versus-host disease (GVHD), this trend is not expected to cease. Despite this improvement in peritransplant and immediate post-transplant survival, life expectancy for patients who survive more than 5 years post-transplant is approximately 30% lower than the general population, regardless of age [8]. This excess mortality has been attributed to the many long-term complications of allogeneic HSCT, including chronic GVHD, infection, and end-organ dysfunction, which may affect the respiratory, endocrine, hepatic, skeletal, ophthalmologic, renal, and cardiovascular systems [9].

Cardiovascular disease (CVD) is one of the more significant long-term complications of allogeneic HSCT, contributing to considerable morbidity and mortality [10-14]. Risk factors for CVD in the general population include age, hypertension, smoking, diabetes, and dyslipidemia [15]. Hypertension and smoking are the leading risk factors in terms of attributable mortality (13% and 9% of annual global deaths, respectively) [16]. However, these risk factors tend to cluster together, and dyslipidemia is estimated to be responsible for approximately 2.6 million deaths (4.5% of attributable global deaths) and one third of ischemic heart disease globally [16]. Management of modifiable cardiovascular risk factors, particularly dyslipidemia, can be challenging in the allogeneic HSCT population. Pharmacologic agents for dyslipidemia are not without serious side effects, and there are a number of clinically significant drug interactions the transplant provider must take into account. In a population particularly prone to adverse reactions and

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polypharmacy, proper management of drug therapy becomes increasingly important.

Growing evidence also shows that statins and other anti-hyperlipidemia medications possess immunomodulatory properties; thus, the choice of lipid-lowering agent may have implications for GVHD outcomes post-transplant [17]. No guidelines exist at this time for the treatment of hyperlipidemia in allogeneic HSCT patients, and because of increasing survival post-transplant, a growing number of these individuals are no longer under the continuous care of transplant centers. Thus, awareness of the magnitude of cardiovascular risk and optimal pharmacotherapy of dyslipidemia in this challenging patient population is crucial. In this review, we summarize literature surrounding the treatment of dyslipidemia in allogeneic HSCT patients, with a focus on pharmacotherapy and the potential for immunomodulation with anti-hyperlipidemia medications.

SCOPE OF THE PROBLEM IN HSCT PATIENTS

In 2011, an international HSCT working group convened to update the recommendations for screening and preventive practices in long-term survivors of HSCT [18]. They noted that compared with other post-transplant complications, CVD is relatively rare. However, the notion that cardiovascular complications after HSCT may be underestimated was acknowledged [18]. Indeed, based on the most recent data available, this appears to be the case. The increased cardiovascular risk among survivors of HSCT was first well described in 2007 by Baker et al. [19]. In a retrospective analysis, 1089 survivors of HSCT were evaluated using 389 siblings as a matched control group. The age- and body mass index–adjusted risk of diabetes mellitus and hypertension were 2 to 3 times higher (odds ratios, 2.31 [95% confidence interval, 1.45 to 3.67] and 3.42 [95% confidence interval, 1.55 to 7.52], respectively) in allogeneic HSCT patients. Another retrospective cohort study of 85 long-term survivors of HSCT found a similar high risk of CVD and metabolic syndrome (according to National Cholesterol Education Program-Adult Treatment Panel III criteria) [13]. The prevalence of metabolic syndrome was approximately double that expected from an age-adjusted general population cohort (29 cases versus 12.8 expected, $P < .0001$). Hypertriglyceridemia was present in 24 of 29 cases of metabolic syndrome in the HSCT group [13].

Not only is the risk of CVD greater in patients post-HSCT, evidence increasingly shows that the onset of CVD in HSCT patients occurs more quickly. A retrospective single-center cohort study by Tichelli et al. [12] found a cumulative incidence of CVD of 22% at 25 years, with a median age at onset of 49 years for the first cardiovascular event. Hyperlipidemia was associated with the development of CVD in a univariate analysis, and in a multivariate analysis the presence of 2 or more cardiovascular risk factors, including hyperlipidemia, was associated with the development of CVD [12]. A larger, multicenter, retrospective cohort study found similar premature adverse cardiovascular outcomes after HSCT, and the median age at onset was 54 [11]. The presence of hyperlipidemia was significantly associated with the incidence of an arterial cardiovascular event within 15 years post-transplant (12% versus 2%, $P = .0001$) [11]. A nested case-control study of 3287 consecutive patients who survived at least 1 year post-transplant also found that post-HSCT hyperlipidemia was a risk factor for development of CVD [14]. Thus, HSCT patients are at risk for premature CVD, and hyperlipidemia is a significant risk factor for this serious post-transplant complication.

An analysis by Kagoya et al. [20] sought to characterize the prevalence and risk factors for dyslipidemia in allogeneic HSCT patients. Of the 194 adult patients followed for a median of 77 months, 42.8% developed hypercholesterolemia and 50.8% developed hypertriglyceridemia. Again, the onset of dyslipidemia was rapid, with the median interval to occurrence of hypercholesterolemia and hypertriglyceridemia of 11 and 8 months post-allogeneic HSCT, respectively. In a multivariate analysis, family history of hyperlipidemia, the incidence of chronic GVHD, chronic liver disease, and steroid use were all independently associated with the development of hypercholesterolemia.

The most comprehensive analysis of the incidence and course of hyperlipidemia post-allogeneic HSCT to date was a retrospective chart review by Blaser et al. [21] of 761 patients who survived >100 days after allogeneic HSCT and had lipid measurements in the post-transplant period. Patients received tacrolimus-based GVHD prophylaxis, and sirolimus was included in 50% of regimens. The incidence of dyslipidemia post-transplant was substantial; 73.4% of patients developed hyperlipidemia and 72.5% hypertriglyceridemia. In a multivariate analysis, being overweight and developing grades II to IV acute GVHD were both associated with post-transplant hyperlipidemia and hypertriglyceridemia. Among those with grades II to IV acute GVHD, 81% with hyperlipidemia and 73% with hypertriglyceridemia were on corticosteroids at the time of peak lipid and triglyceride values. As survival outcomes continue to improve post-HSCT, management of long-term complications becomes increasingly important. Clearly, the preponderance of the literature suggests that the risk of hyperlipidemia and adverse cardiovascular outcomes post-transplant are significant and worthy of treatment consideration.

PATHOPHYSIOLOGY

CVD and coronary artery disease involves a complex interplay between a number of factors, including obesity, dyslipidemia, and inflammation [22]. Adipose tissue increases the production of inflammatory cytokines and chemokines, including monocyte chemotactic protein 1 (MCP-1), tumor necrosis factor (TNF)-α, and IL-6 [23]. Free fatty acids released by adipose tissue also generate reactive oxygen species, leading to the oxidation of low-density lipoprotein (LDL) [23]. The oxidized LDL is ultimately taken up by activated macrophages, leading to the formation of foam cells characteristic of atherosclerotic lesions. Oxidized LDL also promotes endothelial activation, adhesion molecule expression, a reduction in vasodilator production (nitric oxide), and recruitment of platelets and inflammatory cells [23]. Such an inflammatory environment promotes plaque instability, ultimately resulting in plaque rupture, thrombus formation, and infarction [22]. Thus, both inflammation and dyslipidemia contribute significantly to the development of coronary artery disease.

The pathophysiology of dyslipidemia in allogeneic HSCT patients is multifactorial. Allogeneic HSCT patients are on immunosuppression for extended periods of time, and many of these agents are well known for altering lipid homeostasis. Sirolimus, a mammalian target of rapamycin (mTOR) inhibitor used both for the prevention and treatment of GVHD, is associated with a high incidence of hyperlipidemia and hypertriglyceridemia [24]. Sirolimus, in its original studies in renal transplantation, was associated with a 45% to 57% incidence of hypertriglyceridemia and a 43% to 46% incidence of hyperlipidemia at over 1 year post-transplant [24].