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Original Article

Dyslipidemia and lipid-lowering treatment in a hematopoietic stem cell transplant cohort: 25 years of follow-up data

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KEYWORDS:
Dyslipidemia;
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Cardiovascular risk factors

BACKGROUND: Dyslipidemia is common after hematopoietic stem cell transplantation (HSCT). Few data regarding the time course of lipid profiles after HSCT, the effect of multiple transplantations, and efficacy and safety of lipid-lowering treatments are available.

OBJECTIVE: The objective of the study was to determine the prevalence and treatment of dyslipidemia over a 25-year period in a large, single-center cohort.

METHODS: One thousand one hundred ninety-six adult patients (≥16 years) who underwent HSCT during 1973 to 2013 and who survived ≥100 days were studied retrospectively.

RESULTS: The prevalence of dyslipidemia before transplantation was 36% and 28% in the autologous and allogeneic groups, respectively ($P < .001$). Three months after HSCT, the prevalence rose to 62% and 74% ($P < .001$), and at 25 years, it was 67% and 89%. Lipid profiles were similar after first and subsequent transplants. Baseline dyslipidemia (odds ratio [OR] = 2.72), allogeneic transplant (OR = 2.44), and age ≥ 35 years (OR = 2.33) were independent risk factors for dyslipidemia at 1 year. Lipid-lowering treatment was given to 223 (19%) patients, primarily in the form of statins (86%) and was associated with a decrease in total cholesterol from 246 to 192 mg/dL ($P < .01$) and from 244 to 195 mg/dL ($P < .001$) in the autologous and allogeneic groups, respectively. There were 10 cases (4%) of muscle symptoms prompting cessation of lipid-lowering therapy, including 1 case of rhabdomyolysis. The OR for dyslipidemia among patients who suffered a cardiovascular event (conditional logistic regression) was 3.5 (95% confidence interval = 1.6–7.7, $P = .002$).

CONCLUSION: This study confirms that dyslipidemia is a common and long-lasting phenomenon among both allogeneic and autologous HSCT patients. Statins are effective, generally well-tolerated and should be highly recommended for the management of post-HSCT dyslipidemia.

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Introduction

Hematopoietic stem cell transplantation (HSCT) is the treatment of choice for a number of acquired and congenital hematological disorders, the main indications being leukemia and lymphoproliferative disorders.[1–4] Worldwide, the number of transplantations is constantly growing. Furthermore, the considerable improvement in transplantation technology and the introduction of reduced-intensity conditioning regimens has led to an increase in the number of patients with long-term survival and the use of HSCT in older and more morbid patients.[4–8] Therefore, the focus of patient care is no longer solely on the immediate survival after transplantation but increasingly also on the prevention and treatment of late transplant-associated morbidity and mortality.[9] Several studies have found significantly elevated cardiovascular complication and mortality rates in long-term survivors, especially after allogeneic HSCT.[7–13] In the majority of cases, the underlying cause of cardiovascular complications is atherosclerosis. Cardiovascular complications include coronary artery stenosis, myocardial infarction, stroke, and peripheral vascular disease.[11,14] The development of atherosclerosis in general is a slow process, which takes several decades to manifest but is considered to be accelerated in HSCT patients.[11] While the conditioning regimen (especially total body irradiation [TBI]) and graft-versus-host disease (GvHD) are known to directly induce inflammatory reactions in the endothelial cells of the arterial walls,[14,15] common cardiovascular risk factors for atherosclerosis such as hypertension, glucose intolerance, and dyslipidemia appear to be more severe and have a 2- to 5-fold higher incidence in HSCT patients compared to the general population.[7,11,15–18]

Dyslipidemia (or hyperlipidemia) is the common term for disorders of lipoprotein metabolism that result in high total cholesterol (TC), high low-density lipoprotein cholesterol (LDL-C), low high-density lipoprotein cholesterol (HDL-C), and high triglycerides (TG) and is frequently observed in patients after HSCT.[7,10,19–21] Allogeneic transplant patients are at higher risk when compared to autologous HSCT patients.[11,16,18] A general undertreatment of dyslipidemia in HSCT patients has been described previously.[19,20] This might be due to the presumed transient nature of dyslipidemia associated with immunosuppression early after transplantation, a possibly shortened life expectancy, a fear of serious side effects of lipid-lowering agents, and possible drug-drug interactions between statins, fibrates, immunosuppressive agents, and antiinfectives.[7,22,23]

So far, recommendations concerning the management of dyslipidemia after HSCT are based on expert opinion only,[12,24–28] and there are only limited data about the efficacy and safety of lipid-lowering treatment in this population.[20]

Therefore, we aimed to determine the prevalence of dyslipidemia in a large cohort of autologous and allogeneic HSCT recipients over a long follow-up period and to describe the use, efficacy, and safety of lipid-lowering therapy in these patients. A secondary aim was to explore the association between dyslipidemia and the development of cardiovascular events.

Materials and methods

Study population and design

In this retrospective, single-center cohort study, we included consecutive adult (≥16 years) patients who underwent one or more autologous and/or allogeneic HSCTs at the University Hospital Basel between 1973 and 2013 and who survived at least 100 days after the first transplantation. Patients who underwent a subsequent transplantation of the other type were censored at the time point of the subsequent transplantation. Patients who were previously transplanted at another center were excluded as there was no pretransplant information available.

The local ethical committee "Ethikkommission beider Basel" approved this retrospective analysis (EK 190/13).

Data sources and collection

Data were acquired from different sources: information on diagnosis, past medical history, and medication were extracted from the electronic medical information system used by the University Hospital Basel. Laboratory values were available in an electronic form from the year 2000 onwards, while earlier data were completed by searching patient record files.

Lipid values had been obtained at the discretion of the treating physician and were assigned to predefined checkup intervals at baseline (0 months), 3 months, 6 months, 1 year, 2 years, 5 years, and then every 5 years after transplantation until death, loss to follow-up, or completion of data collection at June 18, 2016. Maximum deviations of 20% to the according time interval were tolerated, other than at baseline where only measurements taken before transplantation were recorded. Patients who underwent subsequent HSCTs were treated in 2 different manners according to the type of analysis being performed: Data were allocated based on the date of the first transplantation for general data description analyses, whereas data collection restarted at baseline for each retransplantation for the analysis of lipid profiles. This was to prevent bias, which may have resulted from counting patients who underwent multiple transplantations more than once.

Parameters and definitions

Blood samples are normally drawn after a fasting period of 9 to 12 hours, and an enzymatic test is used to measure the values for TC, HDL-C, and TG, while LDL-C is indirectly estimated using the Friedewald equation.[29] Upper limits for normal values were ≥ 200 mg/dL for TC and TG, ≥ 140 mg/dL for LDL-C, and ≤ 40 mg/dL for HDL-C. In