Dyslipidemia after allogeneic hematopoietic stem cell transplantation: evaluation and management

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Currently, approximately 15 000 to 20 000 patients undergo allogeneic hematopoietic stem cell transplantation (HSCT) annually throughout the world, with the number of long-term survivors increasing rapidly. In long-term follow-up after transplantation, the focus of care moves beyond cure of the original disease to the identification and treatment of late effects after HSCT. One of the more serious complications is therapy-related cardiovascular disease. Long-term survivors after HSCT probably have an increased risk of premature cardiovascular events. Cardiovascular complications related to dyslipidemia and other risk factors account for a significant proportion of late nonrelapse morbidity and mortality. This review addresses the risk and causes of dyslipidemia and impact on cardiovascular complications after HSCT. Immunosuppressive therapy, chronic graft-versus-host disease, and other long-term complications influence the management of dyslipidemia. There are currently no established guidelines for evaluation and management of dyslipidemia in HSCT patients; in this review, we have summarized our suggested approach in the HSCT population. (Blood. 2010;116(8):1197-1204)

Introduction

Allogeneic hematopoietic stem cell transplantation (HSCT) is recognized as an effective treatment for hematologic malignancies and some nonmalignant diseases. Advances in transplantation techniques and supportive care have resulted in a significant improvement in survival, such that long-term survival has now become an expected outcome for patients undergoing HSCT. The list of late complications is increasing, with longer follow-up times and improved knowledge of late effects; in theory, any organ can be the target of a late event. Therefore, knowledge about late complications after HSCT has become increasingly important, particularly because there has been liberalization in the indications for transplantation with respect to the age of the patient, the type of the donor, and the indication for the transplantation.

In the general population, without history of HSCT, cardiovascular disease remains the leading cause of mortality in the United States and the United Kingdom. Lipid abnormalities, including elevated low-density lipoprotein cholesterol (LDL-C) as well as elevated triglycerides and reduced levels of high-density lipoprotein cholesterol (HDL-C), contribute to cardiovascular risk. Other significant risk factors include age, hypertension, diabetes, smoking, family history, and markers of inflammation, including highsensitivity C-reactive protein (hs-CRP). Multiple studies have shown increased prevalence of cardiovascular risk factors in survivors of allogeneic HSCT, and investigators have begun to examine cardiovascular outcomes in this population. As post-HSCT survival has increased, management of cardiovascular risk and other long-term sequelae of HSCT are becoming ever more important. In this review, we summarize the current knowledge of cardiovascular risk factors and outcomes in HSCT patients, and we focus on the evaluation and management of dyslipidemia in the HSCT patient.

Cardiovascular outcomes in HSCT patients

Among patients who survive at least 2 years after transplantation, approximately 70% of autologous HSCT and 80% of allogeneic HSCT patients are expected to become long-term survivors. After 2 years of posttransplantation survival, relative mortality rates decrease over time but still remain elevated at 15 years after transplantation with a standardized mortality ratio of 2.9 at 15 years. In allogeneic HSCT patients followed for an average of 9.5 years from transplantation, relapse of primary disease and chronic graft-versus-host disease (GVHD) remained the first and second most frequent causes of late death, with 3% of observed deaths resulting from cardiac causes. The risk of premature death resulting from cardiac complications was 2.3-fold higher compared with the United States general population. A recent long-term outcome study after allogeneic HSCT found a coronary artery disease (CAD) incidence of 2.2% and a peripheral vascular disease incidence of 1.9% among 369 patients who survived at least 2 years disease-free, from an original cohort of 429 patients. CAD was the cause of death for 5% of the 60 patients who died in the study population.

In a retrospective multicenter study, Tichelli et al assessed the frequency of cardiovascular events after a minimum one-year survival from allogeneic HSCT and reported a cumulative incidence of combined first arterial thrombotic events of 6% at 15 years after transplantation. When patients were further stratified by number of cardiovascular risk factors (defined as hypertension, diabetes, dyslipidemia, increased body mass index, physical inactivity, smoking), cumulative cardiovascular event incidence was
17% for those with more than or equal to 3 risk factors versus 4% for those with less than or equal to 2 risk factors. A separate retrospective cohort study compared incidence and risk factors for cardiovascular events between cohorts of patients after allogeneic versus autologous HSCT. The cumulative incidence of cardiovascular events (CAD, stroke, or peripheral vascular disease) 15 years after allogeneic HSCT was 7.5% compared with 2.3% after autologous HSCT. Adjusting for age, allogeneic HSCT recipients had an almost 7-fold increased relative risk for cardiovascular events compared with autologous recipients. Age at transplantation for allogeneic HCST was also an important factor, with a 20-year cardiovascular event rate of 8.7% for patients transplanted at less than 20 years of age, 20.2% for patients 20 to 40 years of age, and 50.1% for patients 40 to 60 years of age.

Taken together, these studies indicate that allogeneic transplantation patients are at increased risk for cardiovascular complications, and traditional cardiovascular risk factors remain important in their overall risk assessment. In addition to established cardiovascular risk factors, the increased cardiovascular event rates in allogeneic HSCT patients may be related to the effects for GVHD on the artery wall. Although further exploration of this area is needed, potential causative links between GVHD and vascular damage could include increased inflammatory cytokines, such as tumor necrosis factor-α and interleukin-6, or prolonged treatment of GVHD with calcineurin inhibitors and steroids. These agents can promote myocardial hypertrophy and increase risk for hypertension, diabetes, dyslipidemia, and renal disease. Endothelial cell damage is thought to contribute to microvascular damage in the post-HSCT setting. Markers of endothelial damage, including plasminogen-activator inhibitor, cell adhesion molecules, and thrombomodulin, are altered after HSCT. Prolonged endothelial injury could promote atherosclerosis and contribute to more cardiovascular events in long-term survivors after allogeneic HSCT. Long-term survivors after allogeneic HSCT are likely to have an increased risk of premature cardiovascular events irrespective of heterogeneity based on the underlying reason for HSCT. Many patients with hematologic malignancy have been treated with anthracyclines or received chest irradiation before or during HSCT, both of which are known to cause cardiovascular damage. These patients are at increased cardiovascular risk after HSCT.

Estimates of dyslipidemia in different cohorts who survived at least one year after allogeneic HSCT range from 8.9% in a Canadian group to 56% of patients in a United States cohort, 71% of whom remained on immunosuppressive therapy (IST). Taskinen et al reported that hypertriglyceridemia was present in 39% of a small group of 23 survivors of childhood allogeneic HSCT in Finland, excluding patients on active steroid therapy. This was compared with the prevalence of 8% of patients in a group of 13 survivors of acute lymphoblastic leukemia who were treated with chemotherapy but no HSCT. An Italian cohort of 85 survivors of autologous or allogeneic HSCT in complete remission at 5 years demonstrated 34% prevalence of metabolic syndrome; this contrasts with the general population prevalence of approximately 15%. Twenty-four of the 29 patients with metabolic syndrome had hypertriglyceridemia, and 18 had low HDL-C. Many of the aforementioned studies and others have also found clinically and statistically significant increases in glucose dysmetabolism among minimum 1- to 2-year HSCT survivors compared with controls with prior chemotherapy exposure without HSCT or sibling controls. Prevalence of hypertension ranges from 15% to 48.7% of long-term posttransplantation survivors and has been reported to be as high as 70% at one year after HSCT.

The presence or absence of ongoing IST in allogeneic HSCT patients may account for some of the differences in reported risk factor incidence. In an attempt to isolate transplantation- or conditioning-related etiologies for cardiovascular risk factors, some studies exclude patients on ongoing steroid or other IST. Although this will help clarify disease mechanisms, it also may lead to underestimation of the clinical burden of dyslipidemia and other metabolic complications in this patient population.

**Causes of dyslipidemia in transplantation patients**

Common causes of dyslipidemia, such as obesity, and the more common primary genetic lipid disorders, such as familial combined hyperlipidemia (occurring in ~1 of 200 adults) or familial hypercholesterolemia (occurring in ~1 of 500 adults), can also be present in HSCT patients. Significant alcohol intake can raise serum triglycerides and should be assessed in patients with dyslipidemia. Uncontrolled diabetes mellitus can cause marked elevations in cholesterol and triglycerides and make dyslipidemia refractory to drug therapy. Complications of the primary disease, treatment, or transplantation can worsen dyslipidemia. Hypogonadism is common in patients treated in childhood and ovulatory failure common in adult female HSCT patients. Hypogonadism and growth hormone deficiency may predispose to insulin resistance, the metabolic syndrome, and related lipid abnormalities. Hypothyroidism occurs in up to 45% of post-HSCT patients and can promote diastolic hypertension and dyslipidemia. Nephrotic syndrome can also cause significant dyslipidemia or worsen a preexisting genetic lipid disorder.

Chronic GVHD of the liver, when it results in severe cholestatic liver disease, has also been associated with severe hypercholesterolemia in adult and pediatric allogeneic HSCT patients. These patients can have marked elevations in serum cholesterol levels, thought to be caused by intrahepatic cholestasis, reflux of bile lipoproteins into the bloodstream, and subsequent formation of lipoprotein X, an abnormal lipoprotein seen in cholestatic liver disease. Complications of extreme hypercholesterolemia (total

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**Dyslipidemia and other cardiovascular risk factors in HSCT patients**

A cohort analysis based on the Bone Marrow Transplant Survivor Study showed a 3.65-fold higher prevalence of diabetes and 2.06-fold higher prevalence of hypertension compared with a group of siblings, matched for age, sex, race, and body mass index. Allogeneic HSCT recipients were also more likely to develop hypertension (odds ratio = 2.31) compared with autologous recipients. In the aforementioned retrospective cohort study of allogeneic and autologous HSCT patients, the allogeneic group had significantly higher risk of new-onset dyslipidemia (relative risk = 2.31) and hypertension (relative risk = 2.5) compared with the autologous group. The metabolic syndrome is a clustering of cardiovascular risk factors characterized by abdominal obesity, dyslipidemia, hypertension, and elevated fasting glucose. A recent cross-sectional study of 86 adult allogeneic HSCT patients showed a 49% prevalence of metabolic syndrome, a 2.2-fold increase compared with a group of 258 age- and sex-matched controls.

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cholsterol > 1000 mg/dL) in this setting can include retinal cholesterol thromboembolism and pulmonary cholesteroloma.20

Drugs used to treat GVHD are also important causes of dyslipidemia. Dyslipidemia occurs in 45% to 80% of solid-organ transplantation patients on immunosuppressive therapy.23 Among solid-organ transplantation patients, risk factors for dyslipidemia include age, proteinuria, obesity, antihypertensive medication use, dosage of glucocorticoids (with increasing risk related to increasing cumulative dose), use of cyclosporine, and use of sirolimus.23 Glucocorticoids can directly affect lipid metabolism pathways and also may indirectly increase lipid levels by promoting weight gain and hyperglycemia.23 Changes in the lipid profile can include increased VLDL, total cholesterol, and triglyceride levels and decreased HDL-C levels.24-26

Cyclosporine is thought to inhibit bile acid synthesis, bind to and block the LDL receptor, and reduce activity of lipoprotein lipase while increasing activity of hepatic lipase, all of which can promote increases in LDL-C.26,27 Nontransplantation subjects receiving cyclosporine for other indications exhibit increased LDL-C.25 It has been shown to raise total cholesterol and LDL-C in recent study of renal transplantation patients with stable renal function26 and to increase lipoprotein (a) levels in renal transplantation recipients.27 Cyclosporine can also inhibit prednisone metabolism and exacerbate the glucocorticoid effects in patients treated with both agents.27

FK506 (tacrolimus) has been associated with increased lipid levels when given with a corticosteroid; FK506 has shown less frequent and milder effects on lipids compared with cyclosporine27,28 and can allow reduction of steroid dose in combined therapy.23 In solid organ patients, sirolimus has been shown to raise total cholesterol and triglyceride levels, with delay of 4 weeks in return to baseline levels after discontinuation of the drug.23 As many as 49% of liver transplantation and 40% of renal transplantation patients on sirolimus develop hyperlipidemia.27 Mycophenolate mofetil has not been shown to have any direct effects on lipoprotein metabolism or induce hyperlipidemia independent of other agents.28 There is also no apparent adverse effect of azathioprine on lipids.29 Steroids and cyclosporine can also exacerbate other cardiovascular risk factors, such as hypertension and glucose dysmetabolism. Tacrolimus and sirolimus can also have significant detrimental effects on glucose metabolism.27 Interactions between lipid-lowering drugs and immunosuppressants must be carefully considered in the therapeutic approach. Marked hypertriglyceridermia in particular is also associated with risk of pancreatitis. A total of 1% to 4% of pancreatitis cases in the United States are the result of hypertriglyceridermia, usually with serum levels more than 1000 mg/dL.29

In summary, complications of HSCT, such as chronic GVHD, can contribute directly to dyslipidemia by the mechanisms discussed in this section. It is not yet known whether other features inherent to HSCT cause dyslipidemia. In our clinical experience, immunosuppressant agents are the most common cause of significant secondary dyslipidemia in the HSCT population, followed by uncontrolled diabetes. Primary genetic dyslipidemias are also common and can be identified by medical history and review of pre-HSCT lipoprotein profiles. Considering and addressing the factors discussed in this section can also facilitate treatment, particularly in refractory dyslipidemia cases.

Lipid and cardiovascular risk assessment in the transplantation patient

Joint recommendations for monitoring long-term survivors of HSCT by the European Group for Blood and Marrow Transplantation/Center for International Blood and Marrow Transplant Research/American Society for Blood and Marrow Transplantation suggested that, at a minimum, cholesterol and HDL-C levels should be checked at least every 5 years for men starting by age 35 and women starting by age 45. It was further recommended that screening should start at age 20 in smokers, patients with diabetes, or patients with a family history of heart disease. Abnormalities (total cholesterol > 200 mg/dL or HDL-C < 40 mg/dL) should be followed up with a full fasting lipoprotein profile.30 However, these recommendations were published in 2006, before several important papers on late cardiovascular events as reviewed in “Cardiovascular outcomes in HSCT patients,” and should be updated to reflect the new data. Our recommendations based on our clinical experience are summarized in Table 3.

Dyslipidemia should be assessed with a lipid profile after a 9- to 12-hour fast. Traditionally, LDL-C has been estimated using the Friedwald formula (LDL-C = total cholesterol − HDL-C − (triglycerides/5)). However, this formula is inaccurate when triglycerides are more than 400 mg/dL. Direct LDL-C measurement is now available in many laboratories and is unaffected by elevations in serum triglycerides. If a direct LDL measurement is not available, clinicians can use non-HDL cholesterol as an alternative measure. Non-HDL cholesterol equals total cholesterol minus HDL-C and estimates the burden of atherogenic apoprotein B-containing lipoproteins. Generally, advanced lipoprotein testing, such as LDL particle number or lipoprotein subfractions, is not required for dyslipidemia assessment in HSCT patients. Given the increased risk of cholesterol and triglyceride increases on immunosuppressive therapy, periodic monitoring for dyslipidemia should be performed, particularly during the acute posttransplantation phase for patients on IST. Patients with preexisting lipid abnormalities or cardiovascular disease (CVD) risk who undergo HSCT should have a fasting lipid profile before transplantation and regularly thereafter, particularly with initiation of IST.

Decisions about using lipid-lowering therapy should incorporate the patient’s overall cardiovascular risk, other comorbidities, type and severity of dyslipidemia, and potential drug interactions. The patient’s proximity to transplantation and use of immunosuppressants should also be considered. HSCT patients can develop dyslipidemia related to IST and other factors in the early posttransplantation phase but can also develop dyslipidemia later, even if IST has been discontinued. Dyslipidemia in both the early and late phases after HSCT may contribute to long-term cardiovascular risk. The most widely used and recommended risk assessment tool is based on data from the Framingham Heart Study and estimates 10-year risk of hard cardiovascular events (myocardial infarction and coronary death). This 10-year CVD risk calculator is accessible from the National Heart, Lung, and Blood Institute website (www.nhlbi.nih.gov) and incorporates age, sex, total cholesterol, HDL-C, current smoking status, systolic blood pressure, diabetes status, and hypertension treatment status.31 The current National Cholesterol Education Program Adult Treatment Panel guidelines (ATP-III, updated in 2004) stratify LDL treatment recommendations based on the patient’s 10-year cardiovascular risk (Table 1). Threshold levels to initiate therapeutic lifestyle changes and pharmacologic therapy vary for the different levels of risk. LDL-C is the primary therapeutic target, with HDL-C and triglycerides as the secondary targets per ATP-III recommendations. As noted above in this section, non-HDL cholesterol can be used as an alternative target when a calculated LDL-C is not available; the non-HDL cholesterol goal is 30 points higher than the recommended LDL-C goal. Patients with known coronary heart disease

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(CHD) or who have one or more “CHD risk-equivalents” (diabetes mellitus, abdominal aortic aneurysm, carotid stenosis, and peripheral arterial disease) are automatically considered to have high risk. Otherwise, patients should have their 10-year risk calculated to determine their risk category (low, moderate, moderately high, or high risk). When using the risk assessment tool, it is preferable to use a baseline lipoprotein profile before initiation of IST after transplantation because drug-induced dyslipidemia can cause an overestimation of 10-year CHD risk. For patients with severe hypertriglyceridemia (>500 mg/dL), the goal is to reduce triglyceride levels to less than 500 mg/dL to avoid risk of pancreatitis.

Although the Framingham risk score has not been validated specifically in the HSCT population, it provides a useful means to estimate cardiovascular risk and guide therapy. Atherosclerosis is a very chronic process and can be present as a subclinical disease in many patients with preexisting risk factors before HSCT. In long-term HSCT survivors, conventional risk factors, such as diabetes, dyslipidemia, and hypertension, are associated with higher risk of cardiovascular events.8

There have been other methods used to estimate CHD risk in patients, including measurement of hs-CRP and coronary artery calcium scoring by computed tomography. Although hs-CRP has been shown to add prognostic value for CHD risk assessment in the general population, it has not been validated in HSCT.32 In the HSCT population, assessment of hs-CRP may be confounded by several factors, including infection, IST, or GVHD. Therefore, hs-CRP measurement should not be used after HSCT for CHD risk stratification. Likewise, although coronary artery calcium scoring can have use in specific clinical situations, it has not been studied in the HSCT population; thus, its clinical value is uncertain.33

No large study has yet been able to define the influence of HSCT on long-term CVD risk. Longer-term lipid treatment will also depend on weighing the possible benefits for CHD risk reduction against their risk of mortality from malignancy or other diseases after HSCT. If long-term recurrence of the underlying disease is thought to be likely within a few years or the patient has reduced life expectancy resulting from complications after HSCT, then higher lipid levels might be tolerated. However, if 5 to 10 years or more life expectancy is anticipated, then management of cardiovascular risk as would be performed for a general population is likely warranted to reduce morbidity and mortality from cardiovascular disease. Although more study is needed, we think the current available evidence suggests that allogeneic HSCT patients over age 40 with one or more risk factors should be considered to have high CHD risk (10-year risk > 20%).

### Management of dyslipidemia in the HSCT patient

There are only 2 treatment goals for lipid-lowering therapy: (1) to reduce risk of future CVD events and (2) to prevent risk of pancreatitis in patients with severe hypertriglyceridemia. There are few published data on management of dyslipidemia in HSCT. However, there are more data in the solid organ transplantation literature, and many issues regarding lipid therapy, including drug-drug interactions, are common between HSCT and solid organ transplantation patients. Although there is robust evidence for improved CVD outcomes in patients treated with lipid-lowering therapy (particularly HMG-CoA reductase inhibitors, or statins) in the general population, the evidence of clinical outcome benefits in transplantation patients is more limited. There are prospective randomized clinical trials showing improved CVD outcomes and good safety with statin therapy in both renal and cardiac transplantation recipients.34,35

After fasting lipids are measured, the patient’s cardiovascular risk should be assessed as indicated in “Lipid and cardiovascular risk assessment in the transplantation patient.” If LDL-C exceeds the goal as defined by National Cholesterol Education Program ATP-III, therapeutic lifestyle change (TLC) should be initiated, and any secondary causes of lipid abnormalities should be addressed. The American Heart Association TLC guidelines recommend less than 7% total calories from saturated fat and less than 200 mg of daily dietary cholesterol. Lifestyle change should also include minimization of trans-fatty acid intake, increased physical activity, and consideration of increased soluble fiber intake (10-25 g/day).36

Patients who develop dyslipidemia in an early or intermediate posttransplantation period may still have increased risk of cardiovascular events over the long term. In these patients who are still taking IST, consideration should be given to whether IST medications can be safely reduced in dose or changed to modify their effects on lipids.3 In patients with low or moderate CHD risk and moderate dyslipidemia, a trial of TLC alone can be used as initial
management. If lipid levels remain above goal for a patient’s risk category, then pharmacologic therapy should be considered with attention to drug interactions. In patients who are no longer on IST and have stabilized in the longer term after transplantation, TLC may be used initially for low to moderate CHD risk and moderate dyslipidemia; however, if response is inadequate, then intensification of therapy should not be delayed. In the absence of ongoing IST or GVHD, treatment of lipids is similar to that of any patient with dyslipidemia.

Pharmacologic agents for dyslipidemia are summarized in Table 2. Statins are the most widely used class of agent, but proper selection of statin preparation and dose is important. Cyclosporine’s metabolism by the cytochrome P450 3A4 is a key factor in drug-drug interactions, as it can raise levels of statins and thus risk for myopathy.37,38 Other inhibitors of CYP3A4, specifically and can be safely coadministered with immunosuppressive drugs,46 but drug levels should be monitored. Bile acid sequestrants can raise triglyceride levels and are contraindicated in patients with hypertriglyceridemia. Ezetimibe was previously reported to interact with cyclosporine to cause 12-fold elevations in ezetimibe levels.49 However, ezetimibe also appear to be metabolized by this pathway.50 Older bile acid sequestrants (cholestyramine and colestipol) should be avoided in patients on IST or those with complex medication regimens because of the potential inhibition of drug absorption.

Table 2. Lipid-lowering agents and considerations in the post-HSCT population

<table>
<thead>
<tr>
<th>Predominant dyslipidemia/drug class</th>
<th>Agent/daily dose range*</th>
<th>Expected effect</th>
<th>Major side effects</th>
<th>Important interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated LDL-C predominant</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HMG-CoA reductase inhibitors</td>
<td>Pravastatin, lovastatin,† or atorvastatin/10-80 mg; fluvastatin/20-80 mg; simvastatin/5-80 mg; rosuvastatin/5-40 mg</td>
<td>↓ LDL-C 30%-45%; ↑ triglycerides 7%-30%; ↑ HDL-C up to 10% (variable by agent)</td>
<td>Myopathy; elevated liver tests</td>
<td>Increased myopathy risk with renal dysfunction and cyclosporine; fibrates; CYP3A4 inhibitors</td>
</tr>
<tr>
<td>Cholesterol absorption inhibitor</td>
<td>Ezetimibe/10 mg</td>
<td>↓ LDL-C 17%</td>
<td>Gastrointestinal upset, elevated liver tests, myalgias (rare)</td>
<td>No major drug interactions</td>
</tr>
<tr>
<td>Bile acid sequestrants</td>
<td>Colesevelam‡/2400-3750 mg</td>
<td>↓ LDL-C 15%-30%; can raise triglycerides</td>
<td>Constipation, dyspepsia</td>
<td>Monitor drug levels in IST</td>
</tr>
<tr>
<td>Hypertriglyceridemia predominant</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Omega-3 fatty acids</td>
<td>Omega-3-acid ethyl esters/2-4 g daily divided bid</td>
<td>↓ triglycerides 35%-45%, ↑ HDL-C 3%, ↑ LDL-C 5%</td>
<td>Gastrointestinal upset, diarrhea</td>
<td>No major drug interactions</td>
</tr>
<tr>
<td>Fibric acid derivatives</td>
<td>Fenofibrate, fenofibric acid/45-200 mg daily; gemfibrozil/600-1200 mg daily divided bid</td>
<td>↓ triglycerides 20%-50%, ↑ HDL-C 10%-20%</td>
<td>Myopathy, elevated liver tests, gallstones, rash; renal dysfunction (fenofibrate)</td>
<td>Use with caution in combination with statins and cyclosporine.</td>
</tr>
<tr>
<td>Mixed hyperlipidemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Niacin</td>
<td>Niacin/500-2000 mg</td>
<td>↓ LDL-C 20%-30%, ↓ triglycerides 35%-55%, ↑ HDL-C 20%-35%</td>
<td>Dyspepsia, flushing, elevated liver tests, ↑ glucose, ↑ uric acid</td>
<td>No major drug interactions</td>
</tr>
</tbody>
</table>

*We recommend submaximal statin dosing in patients on IST agents that may alter metabolism of the statin agents. In general, patients gain only 6% additional LDL-C lowering with each doubling of statin dose.
†Metabolized by CYP3A4.
‡Older bile acid sequestrants (cholestyramine and colestipol) should be avoided in patients on IST or those with complex medication regimens because of the potential inhibition of drug absorption.
Table 3. Suggested approach to lipid management in HSCT patients

**Evaluation**
- Obtain fasting lipid profile before transplantation
- Evaluate CHD risk
  - 1. If patient has CHD or CHD risk equivalent, then manage as high risk with appropriate therapy to reach LDL goal
    - a. Option to consider allogeneic HSCT patients 40 years of age or older as high risk
  - 2. Otherwise, calculate 10-year risk with online risk assessment tool (hp2010.nhlb.nih.gov/atpiii/calculator.asp?usertype=prof) and manage LDL per ATP-III guidelines

**Monitor lipid profiles after HSCT**
- 1. Check lipid profile within 4 weeks after HSCT and then at least every 3 months for patients on IST
- 2. For patients at treatment goal on stable therapy every 6 to 12 months as indicated, or after significant change in IST regimen in patients with dyslipidemia
- 3. If patients develop significant dyslipidemia after HSCT compared with baseline, consider secondary causes of dyslipidemia (IST, diabetes, and hypothyroidism)
- 4. Even patients without dyslipidemia should have lipids monitored every 1 to 2 years after allogeneic HSCT given increased CV risk

**Management**
- If patient has high CHD risk (≥20% 10-year risk), treat dyslipidemia with appropriate agent(s) to meet LDL goal, but monitor clinically if on IST or renal dysfunction
- In patients with low (<10%) or moderate CHD risk (10%–20%), consider drug treatment based upon severity of dyslipidemia, estimated prognosis after HSCT, and risks of lipid drug therapy (if on long-term IST for GVHD)
  - 1. In patients with low CHD risk that develop moderate secondary dyslipidemia on IST, this can be managed conservatively if IST will be tapered off
  - 2. Patients with low to moderate CHD risk that develop severe hypertriglyceridemia (>500 mg/dL) should be treated to prevent pancreatitis

- Consider referral to a lipid specialist for the following:
  - 1. Severe dyslipidemia (total cholesterol >300 or LDL >180, triglycerides >500-1000)
  - 2. Patients with dyslipidemia refractory to treatment and not meeting goals
  - 3. Patients with intolerance or contraindications to lipid-lowering therapy
  - 4. Patients requiring combination lipid therapy, particularly in the setting of IST
  - 5. Patients needing individualized cardiovascular risk assessment because of strong family history of premature CHD or other factors

Summary and recommendations

Dyslipidemia and other cardiovascular risk factors are increased in allogeneic HSCT patients. The risk for allogeneic transplantation exceeds that for autologous transplantation, even when autologous transplantation patients are older; some of the increased risk is related to IST, but other, unknown mechanisms may also contribute. As post-HSCT survival improves, prevention and treatment of longer-term morbidities such as cardiovascular disease is gaining importance, and management of dyslipidemia is an important factor in managing cardiovascular risk. LDL-C is the primary focus for cardiovascular risk reduction, although treatment should also be initiated for severe hypertriglyceridemia (>500 mg/day) to reduce the risk of pancreatitis. There are currently no established guidelines for evaluation and management of dyslipidemia in HSCT patients, so we have summarized our suggested approach in the HSCT population based on our clinical experience (Table 3). Recommendations from a National Heart, Lung, and Blood Institute clinical advisory on the use and safety of statins provides useful guidelines for monitoring statin therapy. Although creatine phosphokinase (CPK) levels should be checked at baseline, routine monitoring of CPK in asymptomatic patients on statins is not recommended because mild elevations in CPK are often not clinically significant. However, patients should be asked about muscle symptoms at follow-up, and a CPK should be checked if the patient has symptoms concerning for myopathy. Aspartate aminotransferase and alanine transaminase should be monitored at baseline and within 12 weeks of starting therapy. Generally, transaminase elevations less than 3 times the upper limit of normal do not represent a contraindication to statin therapy. Because mild transaminase elevations are common in patients after HSCT, these can simply be monitored and therapy continued as long as they are not progressively increasing.
At this time, it is unclear how HSCT influences CVD risk, so other comorbidities should be taken into account to determine LDL-C goals using the National Cholesterol Education Program ATP-III guidelines. Patients who are still on IST are more likely to have dyslipidemia and also are at risk for drug interactions. Statin therapy is first-line treatment for LDL-C–predominant dyslipidemia. Given their established role in cardiovascular risk reduction in the general population, they should be considered first-line therapy for dyslipidemia in HSCT patients. Selection of the appropriate statin preparation and dose are important to minimize side effect risk. Niacin, ezetimibe, or colestevamay be considered as second-line agents if LDL-C goals are not met. For mild to moderate hypertriglyceridemia, we favor omega-3 fatty acids because of their excellent safety and tolerability. Fibrates should be reserved for more severe hypertriglyceridemia in patients on IST and used with caution in patients requiring statin therapy or with renal dysfunction. Niacin may be considered as a second agent with statins or for treatment of elevated triglycerides and low HDL in patients with mixed hyperlipidemia.

**Authorship**

Contribution: B.N.S. planned the review; and M.L.G., B.N.S., and J.B.B. contributed to the writing of the manuscript.

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