Metabolic syndrome and cardiovascular disease following hematopoietic cell transplantation: screening and preventive practice recommendations from CIBMTR and EBMT

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Abstract

Metabolic syndrome (MetS) is a constellation of cardiovascular risk factors that increases the risk of cardiovascular disease, diabetes mellitus, and all cause mortality. Long-term survivors of hematopoietic stem cell transplantation (HCT) have a substantial risk of developing MetS and cardiovascular disease, with the estimated prevalence of MetS being 31-49% amongst HCT recipients. While MetS has not yet been proven to impact cardiovascular risk after HCT, an understanding of the incidence and risk factors for MetS in HCT recipients can provide the foundation to evaluate screening guidelines and develop interventions that may mitigate cardiovascular-related mortality. A working group was established through the Center for International Blood and Marrow Transplant Research and the European Group for Blood and Marrow Transplantation with the goal to review literature and recommend practices appropriate to HCT recipients. Here we deliver consensus recommendations to help clinicians provide screening and preventive care for MetS and cardiovascular disease among HCT recipients. All HCT survivors should be advised of the risks of MetS and encouraged to undergo recommended screening based on their predisposition and ongoing risk factors.

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Introduction

Advances in hematopoietic cell transplantation (HCT) and supportive care have led to substantial improvements in transplant outcomes and an increased number of long-term HCT survivors [1]. Transplant survivors are at considerable risk for developing significant late effects and experience mortality rates higher than the general population [2, 3]. One challenge faced in the post-HCT setting is the development of metabolic syndrome (MetS), with reported prevalence rates of 31-49% [4-8]. HCT recipients are predisposed to develop MetS through several mechanisms, including conditioning regimen-mediated damage to the neurohormonal system and vascular endothelium, as well as the immunological and inflammatory effects of allografting (including subsequent graft-versus-host disease (GVHD) and its therapy) [4]. Individuals in the general population with MetS are twice as likely to develop cardiovascular disease than those without MetS [9]. A better understanding of MetS following HCT may prove to be significant, as HCT survivors are known to be at increased risk for cardiovascular morbidity and mortality. In the Bone Marrow Transplant Survivor Study (BMTSS), the risk of premature cardiovascular-related death following HCT was found to be increased 2.3-fold compared to the general population [2, 3]. Similarly, others have reported the risk of cardiovascular hospitalizations and mortality to be increased by 3.6-fold in HCT recipients compared to the general popuation [10].

Intensive chemotherapy and radiation have been associated with MetS and contribute to the development of this syndrome post-HCT, especially in heavily pre-treated populations [11, 12]. MetS has not yet been proven to impact cardiovascular risk after HCT. However, an understanding of the incidence and risk factors for MetS and cardiovascular disease following HCT provide the foundation to evaluate screening guidelines and develop interventions that may mitigate cardiovascular-related mortality. Therefore, a collaboration was established between the Center for International Blood and Marrow Transplant Research (CIBMTR) Late Effects and Quality of Life Working Committee and the European Group for Blood and Marrow Transplantation (EBMT) Complications and Quality of Life Working Party with the goal to review literature, including previously published guidelines for screening and preventive practices for HCT survivors [13-15]. We subsequently provide specific screening and preventive practice recommendations for MetS and cardiovascular disease appropriate to HCT recipients based on published evidence and expert opinion.

Metabolic syndrome

MetS is a cluster of interrelated factors that increases the risk of cardiovascular disease, diabetes mellitus (DM), and all cause mortality [16-18]. The International Diabetes Foundation (IDF) estimates that 25% of the world's adult population has MetS [19]. The four core clinical measures are increased body weight/visceral adiposity, elevated lipids, raised blood pressure (BP), and hyperglycemia/insulin resistance (IR) [20]. The individual diagnostic criteria of MetS have varied over

time according to the different definitions applied. The diagnostic criteria of the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATPIII) [21], the IDF [22], the American Heart Association (AHA) [9] and the World Health Organization (WHO) [23] are shown in **Table 1.** A comparison of various definitions in terms of their predictive value established that the prevalence of MetS was significantly greater when using the criteria of the AHA and IDF compared with the NCEP ATPIII definition [24]. However, the risks of cardiovascular events and death were markedly greater for participants who satisfied any of the criteria for diagnosis of MetS compared with healthy individuals. This supports other reports that found agreement between MetS components and cardiovascular risk factors in the general population [25, 26].

Abdominal obesity

Obesity, defined as a body mass index (BMI) ≥30 kg/m^2, affects 35% of adults in the United States [27] and 10-30% of adults in Europe [28]. Obese persons have a higher risk of developing serious medical conditions, including hypertension (HTN), dyslipidemia, type 2 DM, coronary heart disease (CHD), and ischemic stroke, and have a higher mortality than the non-obese population [29]. However, BMI is an insufficient measure of abdominal obesity. Waist circumference, which emphasizes visceral adipose deposits, is preferentially used in the evaluation of abdominal obesity when defining MetS (see **Table 1**) as this distribution of fat accumulation independently confers cardiometabolic risk [30, 31]. Yet, as studies reporting waist circumference at the time of and following HCT are limited, BMI may act as a possible surrogate.

BMI ≥35 kg/m^2 (severely obese) is part of the HCT-specific Comorbidity Index since 2005, as this was determined to be a risk factor for increased non-relapse mortality (NRM) [32-35]. While pre-transplant obesity can influence body composition following HCT, changes in waist circumference can be seen independent of pre-existing obesity. Despite what may be a normal BMI, HCT survivors are at an increased risk to develop sarcopenic obesity (increase in percent fat mass, decrease in lean body mass), which can significantly contribute to IR [36, 37]. A longitudinal study using dual X-ray absorptiometry (DXA) to calculate body fat mass index (BFMI) in 82 patients found the prevalence of a high BFMI was greater at 2-3 years following allo-HCT than in healthy controls [38]. Corticosteroids, which remain the first line treatment of GVHD, contribute to sarcopenic obesity by promoting muscle atrophy and may contribute to obesity in the early post-HCT period [39, 40]. Robust data on the changes in abdominal obesity following autologous HCT (auto-HCT) are lacking. One study evaluated metabolic and body composition changes in 32 patients with multiple myeloma who had received three lines of intensive treatment, including at least one HCT. At a median duration of 6 years from diagnosis, DXA identified sarcopenic obesity in 65% of patients [41]. Importantly, the development of sarcopenic obesity following HCT has yet to be independently associated with increased cardiovascular mortality. In the pediatric population, a cross-sectional study evaluating 54 allo-HCT survivors and 894 healthy participants found a deficiency

in lean mass (as identified by DXA) as compared to fat mass in HCT survivors [42]. A prospective, descriptive, cross-sectional study evaluating children and adolescents for the development of MetS post-HCT found that 73% of individuals with this diagnosis had a characteristic of abdominal obesity (abdominal circumference >75th percentile by age and gender) [5].

Screening and preventive recommendations

The United States Preventive Services Task Force (USPSTF) and the National Heart, Lung, Blood Institute (NHLBI) recommend screening for obesity in all adults and children >2 years of age, though no recommendation is made regarding appropriate intervals for screening. Current guidelines for HCT recipients do not provide specific screening recommendations for abdominal obesity, though education and counseling regarding regular exercise, healthy weight, and dietary counseling are encouraged [14, 15]. Given the increase in abdominal obesity that can occur after HCT, clinicians should consider monitoring body composition at each visit, with regular measurement of height, weight, and waist circumference (at least yearly). Based on what is known in other populations, we recommend that patients with a BMI ≥30 kg/m^2, waist circumference >102 cm (>40 inches) in men or >88 cm (>35 inches) in women, or significant increases in either of these measurements should be considered for intensive, multicomponent behavioral interventions. DXA may be used to assist evaluation and monitoring of changes in body composition in survivors of HCT.

Dyslipidemia

Dyslipidemia, defined as elevated levels of total cholesterol, low-density lipoprotein (LDL) cholesterol or triglycerides, or low levels of high-density lipoprotein (HDL) cholesterol, is an important risk factor for CHD and ischemic stroke [43, 44]. The prevalence of dyslipidemia is high in the general population: in 2000, approximately 25% of adults in the United States had total cholesterol greater than ≥240 mg/dL (≥6.2 mmol/L) or were taking lipid-lowering medication [45]. A high prevalence of dyslipidemia has also been reported in European countries [46, 47]. Of the various dyslipidemias, low HDL (<40-50 mg/dL, <1.0-1.3 mmol/L) and hypertriglyceridemia (>150 mg/dL, >1.7 mmol/L) have been incorporated into the diagnostic criteria of MetS (see **Table 1**).

Survivors of allo-HCT are at an increased risk of post-transplant dyslipidemia. In a retrospective cohort study comparing incidence and risk factors for cardiovascular events, allo-HCT recipients had significantly higher risk of new-onset dyslipidemia (RR: 2.31; 95% CI, 1.15 to 4.65) compared to auto-HCT recipients [48]. Single institution studies have estimated the incidence of hypercholesterolemia and/or hypertriglyceridemia following allo-HCT to be 43-73% [49, 50]. The onset of dyslipidemia post-HCT can be rapid, with the median interval to development of hypertriglyceridemia and hypercholesterolemia being 8 and 11 months following allo-HCT, respectively, in one single center experience [49]. Factors predicting development of post-HCT dyslipidemia include family history of hyperlipidemia, obesity, high-dose total body irradiation (TBI), grade II-

IV acute GVHD, chronic GVHD, and chronic liver disease [5, 8, 49-51]. In addition, immunosuppressant medications (e.g., sirolimus, calcineurin inhibitors, corticosteroids) not only increase lipid levels but also lead to significant drug-drug interactions with 3-hydroxy-3-methyl-gutaryl (HMG)-CoA reductase inhibitors (statins) via the cytochrome p450 pathway [52, 53]. Data regarding the incidence of dyslipidemia following auto-HCT are limited. In a single center analysis evaluating late post-HCT cardiovascular complications in 1379 patients, which included both auto- and allo-HCT recipients, 1-year post-HCT dyslipidemia requiring treatment was associated with an increased risk for stroke (HR 7.4; 95% CI, 1.2-47) [54]. In the pediatric population, the risk of hypercholesterolemia is high in childhood cancer survivors who underwent auto-HCT (HR = 3.2; CI 1.7-5.9) [55].

Screening and preventive recommendations

The USPSTF strongly recommends screening for lipid disorders every 5 years in men ≥35 years, women ≥45 years, and persons ≥20 years at increased risk for CHD, while the NHLBI recommends screening in children between the ages of 9-11 years or earlier in those with family history. Current guidelines for HCT recipients recommend similar screening practice for dyslipidemia amongst the general population [14, 15]. We recommend standard-risk patients (including auto-HCT recipients without personal risk factors) should follow these guidelines. However, early onset of dyslipidemia following allo-HCT is not uncommon, especially in high-risk patients. Thus, we propose early assessment of exposures and risk factors in all HCT patients. For recipients of allo-HCT, we suggest an initial lipid profile 3 months after HCT. For high-risk patients with ongoing risk factors (including those on sirolimus, calcineurin inhibitors, corticosteroids), we suggest repeat evaluation every 3-6 months. Non-pharmacologic management of dyslipidemia primarily involves lifestyle modifications such as diet (low saturated fat and low cholesterol), exercise (or other regular physical activities), weight reduction, smoking cessation, and limiting alcohol intake. Although not validated amongst HCT survivors, we recommend use of the Framingham risk score (http://cvdrisk.nhlbi.nih.gov) to assess cardiovascular risk and guide therapy decisions [43]. The safety of lipid-lowering agents must be considered in the pediatric population, as the AHA recommends considering drug therapy for high-risk lipid abnormalities in boys ≥10 years of age and after onset of menses in girls, preferably after a 6 to 12 month trial of saturated fat- and cholesterol-restricted dietary management [56].

Hypertension

HTN, defined as a systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg, is a worldwide epidemic affecting approximately ~25% of adults [57]. Of note, the blood pressure criteria used in most definitions of MetS is systolic BP ≥135 mmHg or diastolic BP ≥85 mmHg (or drug treatment for HTN) (see **Table 1**), which is classified as pre-hypertension according to the report from the Eighth Joint National Committee (JNC 8) [58].

An analysis of the BMTSS showed that after adjustment for age, sex, race, and BMI, allo-HCT recipient were 2.06 times (95% CI, 1.39-3.04) more likely to report HTN as compared to sibling donors or auto-HCT recipients, who had a similar risk (OR, 0.96; 95% CI, 0.65-1.44) [59]. Similarly, a retrospective, single-institution evaluation of 265 long-term transplant survivors reported that allo-HCT recipients have an increased risk of HTN (RR: 2.50; 95% CI, 1.19 to 5.27) compared to auto-HCT patients [48]. A direct cause and effect relationship of conditioning regimen, acute or chronic GVHD and HTN was not established [59]. Two large retrospective studies did not show a significant difference in the incidence of HTN in allo-HCT recipients with or without GVHD [59, 60]. It appears that HTN is related to use of certain GVHD therapies (e.g., calcineurin inhibitors, steroids) rather than GVHD induced pro-inflammatory cytokine response and endothelial damage. Although pediatric patients are less likely than adults to have pre-transplant HTN as well as any risk factors for HTN, an analysis of 1-year survivors of allo-HCT found a similar incidence of post-HCT HTN in adult (68%) and pediatric (73%) HCT survivors [61]. In multivariate analyses, exposure to cyclosporine increased the risk of HTN post-HCT (RR: 1.6; 95% CI, 1.1-2.5), but only within the first 2 years, suggesting this may revert once medications are stopped.

Screening and preventive recommendations

The USPSTF recommends BP assessment every 3 to 5 years in adults aged 18-39 years with normal BP (<130/85 mm Hg) who do not have other risk factors and annually in adults aged ≥40 years and for those who are at increased risk for high BP. In children, the NHLBI recommends BP assessment yearly after the age of 3 years, interpreted for age, sex, and height. Current guidelines for HCT recipients recommend at least annual BP assessment in children and BP assessment every other year in adults [14, 15]. We recommend BP assessment for HCT recipients at every clinic visit (at least yearly). The JNC 8 report recommends initiating pharmacologic treatment for BP of ≥150/≥90 mmHg in persons ≥60 years of age (to a BP goal of <150/<90 mmHg) and for BP of ≥140/≥90 in persons 30-59 years of age (to a BP goal of <140/<90) [58]. In the absence of HCT-specific evidence, these goals can be used to guide management of HCT recipients, but other factors such as end organ compromise (cardiac or renal failure) and therapy with calcineurin inhibitors also need to be taken into account.

Insulin resistance/diabetes mellitus

DM, which affects almost 10% of the adult population worldwide, is characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of DM is associated with long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels. The American Diabetes Association (ADA) defines DM as a fasting plasma glucose ≥126 mg/dl (≥7 mmol/L), a 2–hour plasma glucose ≥200 mg/dl (≥11.1 mmol/L), or a hemoglobin A1C (HbA1C) ≥6.5% [62]. Impaired fasting glucose (IFG, fasting glucose 100-126 mg/dL (5.6-7 mmol/L)) or DM are

used in most definitions of MetS (**Table 1**). The treatment of DM may reduce the progression of microvascular and cardiovascular disease [63-66]. Although randomized trials have failed to demonstrate an unequivocal benefit, the identification of patients by screening allows for earlier intervention with potential reduction in complications [67, 68].

While hyperglycemia and impaired glucose tolerance (IGT) are well-recognized complications of cancer and GVHD treatment (corticosteroids), data regarding the long-term risk of DM in HCT survivors are limited [69]. In the BMTSS, both allo-HCT (OR, 3.65; 95% CI, 1.82-7.32) and auto-HCT (OR: 2.03; 95% CI, 0.98-4.21) recipients were more likely to report DM than sibling donors [59]. The incidence of post-HCT DM was 30% among 1-year allo-HCT recipients in both adult and pediatric populations [61]. In this study, exposure to high-dose corticosteroids (cumulative prednisone dose of > 0.25 mg/kg/day) increased the likelihood of developing DM (RR, 3.6; 95% CI, 1.7-7.5) and for having persistent DM at 2 years post-HCT (RR, 4.1; 95% CI, 1.0-18.2). While data regarding the incidence of IR in survivors of adult HCT are lacking, the incidence of IR for pediatric HCT survivors has been estimated to be 10-52% in single center studies [70-73]. These reports suggest an increased risk for IR/DM in survivors of both allo- and auto-HCT compared to patients treated with chemotherapy alone or untreated siblings, even when off immunosuppressive treatments. Preliminary data from a cross sectional study including 151 HCT survivors (76.8% allo-HCT) and 92 sibling controls found HCT survivors who had received TBI conditioning to be significantly more likely to have IR than their sibling controls, but there was no increased risk of IR for those patients who had a history of acute or chronic GVHD (personal communication, Baker KS). Multiple studies found high-dose TBI as a risk factor for IR and IGT, in addition to older age and lipodystropic body type [72-75]. While data have not demonstrated an increased risk of diabetes to be directly associated with history of GVHD, further study is warranted.

Screening and preventive recommendations

The most common tests to screen for diabetes are fasting plasma glucose, two-hour plasma glucose during an oral glucose tolerance test, and HbA1C. The USPSTF recommends screening for abnormal blood glucose (HbA1C, fasting plasma glucose or oral glucose tolerance test (OGTT)) every 3 years in adults aged 40-70 years who are overweight or obese. The NHLBI recommends screening with a fasting glucose every 2 years after the age of 10 years in overweight children with other risk factors. Current guidelines for HCT recipients recommend screening for type 2 DM every 3 years in adults aged ≥45 years or in those with sustained higher BP (>135/80 mm Hg) and fasting glucose at least every 5 years pediatric survivors [14, 15], which should be appropriate for standard-risk patients. For high-risk patients with ongoing risk factors (including those on systemic corticosteroids), we recommend screening for abnormal blood glucose (HbA1C or fasting plasma glucose) 3 months after HCT with repeat evaluation every 3-6 months. OGTT may be used to evaluate abnormal screening results. For patients with IFG, we encourage weight reduction and

increased physical activity while patients with type 2 DM should implement lifestyle therapy and pharmacotherapy, if necessary, to achieve near-normal HbA1C (<7%).

Coronary heart disease

More people die from cardiovascular disease each year than from any other cause. Cardiovascular disease is caused by disorders of blood vessels and is closely related to atherosclerosis, where endothelial lesions occur up to decades before clinical manifestations [76, 77]. Risk factors for arteriosclerosis in the general population are well established and include smoking, arterial HTN, obesity, DM, dyslipidemia, familial history of CHD, physical inactivity, male gender and elevated C-reactive protein [78].

Several studies have attempted to assess the incidence of cardiovascular disease after HCT, with or without a comparison to a control population. A retrospective multicenter EBMT analysis showed that 3.6% of long-term allo-HCT survivors transplanted between 1990 and 1995 had a cardiovascular event in at least one arterial territory observed [79]. The cumulative incidence of a first cardiovascular event 15 years after HCT was 6% (95% CI, 3%-10%). One study reported a cumulative incidence of 7.5% for the first cardiovascular event at 15 years post allo-HCT, as compared with 2.3% post auto-HCT [48]. In multivariate analysis, allo-HCT, in addition to at least 2 of 4 cardiovascular risk factors (HTN, dyslipidemia, DM, and obesity) was associated with a higher incidence of cardiovascular events (RR: 12.4; P=.02). In a retrospective cohort study, ≥2-year HCT survivors experienced an increased incidence of cardiovascular death (adjusted incidence rate difference, 3.6 per 1000 person-years (95% CI, 1.7 to 5.5) when compared with the general population [10]. In this study, an increased cumulative incidence was also found for ischemic heart disease, cardiomyopathy or heart failure, stroke, vascular diseases, and rhythm disorders and an increased incidence of related conditions that predispose toward more serious cardiovascular disease (HTN, renal disease, dyslipidemia, and DM). In another study, HCT recipients had significantly higher rates of cardiomyopathy (4.0% vs. 2.6%), stroke (4.8% vs. 3.3%), dyslipidemia (33.9% vs. 22.3%) and DM (14.3% vs. 11.7%) (P<.05 for all comparisons) than the general population, though lower rates of ischemic heart disease (6.1% vs. 8.9%; P<.01) [80]. In the BMTSS, survivors of both allo- and auto-HCT were not more likely to report arterial disease, myocardial infarction or stroke than sibling donors [59]. One series, which included 42.7% allo-HCT recipients, reported an incremental increase in 10-year incidence of cardiovascular disease by number of cardiovascular risk factors (4.7% (no factor), 7.0% (one risk factor), 11.2% (≥2 risk factors), P<.01); the risk was especially high (15.0%) in patients with multiple risk factors and pre-HCT exposure to anthracyclines or chest radiation [81]. In the adult population, it is important to acknowledge that an increasing number of older patients are undergoing allo-HCT with reduced intensity conditioning and that future studies are needed to assess the incidence of cardiovascular complications in this population.

In children with acute lymphoblastic leukemia, high-dose TBI and cranial irradiation correlated with multiple adverse cardiovascular factors including central adiposity, HTN, IR and dyslipidemia [82, 83]. Some studies have analyzed the correlation with GVHD and either found a correlation [84] or not [48, 85] and if so, more likely with acute than chronic GVHD [79, 81].

Screening and preventive recommendations

In the general population, a person's 10-year risk for CHD is determined based on age, gender, and conventional CHD risk factors such as smoking, HTN, and dyslipidemia (Framingham risk score, http://cvdrisk.nhlbi.nih.gov)) [86]. Overall, the benefits of screening with resting or exercise electrocardiography (ECG) or for non-traditional risk factors, including coronary artery calcification on electron-beam computerized tomography (EBCT), have not been clearly demonstrated to outweigh harms. The USPSTF recommends against screening with ECG in asymptomatic adults with low risk for CHD and concludes that there is insufficient evidence to assess the balance of benefits and harms of screening with resting or exercise ECG in asymptomatic adults at intermediate- or high-risk for CHD events. Similarly, the USPSTF finds insufficient evidence to assess the balance of benefits and harms of using non-traditional risk factors to screen asymptomatic men and women with no history of CHD to prevent CHD events. Current guidelines for HCT recipients do not provide specific screening recommendations for coronary heart disease [14]. Decisions about screening in adults at increased risk should be made on a case-by-case basis and after careful discussion with the patient about the risks and benefits of screening. Although little data are available about specific interventions in the HCT populations, we recommend a similar approach.

Ischemic Stroke

Stroke is the fourth leading cause of death in the United States, whereas globally it is the second most common cause of mortality and the third most common cause of disability [87, 88]. Globally, stroke incidence from ischemia is 68% and 32% from hemorrhagic stroke (intracerebral and subarachnoid combined) [89]. Pediatric stroke is a top ten cause of death in children, occurring at 11 per 100,000 children per year, with acute ischemic stroke accounting for half of all cases [90-92].

The cumulative incidence of stroke after adult HCT has been reported in single center series to be 1-5% at a median of 4-10 years following HCT [10, 48, 51, 82, 93]. In one study of 3833 HCT survivors of ≥1 year (71.3% allo-HCT), the prevalence of stroke at a median of 10.8 years since HCT was slightly higher than in a matched general population sample (4.8% vs 3.3%) [51]. Reported risk factors for stroke include hyperlipidemia, suboptimal physical activity, HTN treatment before HCT, BMI ≥ 30 kg/m^2 at HCT, and recurrence of the original disease [10, 51, 54]. The risk of stroke did not differ statistically between auto- or allo-HCT, gender, age at HCT, TBI dose, smoking history, donor type, stem cell source, fruit or vegetable intake, and prior cranial radiation [10, 51, 54, 59]. A

history of chronic GVHD was associated with an increased risk of stroke among ≥5-year HCT survivors (OR, 2.0; 95% CI, 1.1-3.6) in one study [51], while it was not statistically associated with risk of stroke in the other studies. Although ischemic stroke is an indication for HCT in sickle cell disease (SCD), reports indicate that there is no increased risk post-HCT in this population. In one report of pediatric SCD patients, 2 had TIAs after allo-HCT but not stroke [94]. Similarly, another study of pediatric SCD matched related allo-HCT patients did not report stroke in those with successful engraftment [95]. Adult SCD may have a higher risk of stroke and allo-HCT studies in the adult population are ongoing.

While the reported incidence of stroke in HCT survivors is low, it may be under recognized due to under reporting. Central nervous system complications – such as stroke, posterior reversible encephalopathy syndrome (PRES) and seizures - also occur frequently in the early post-HCT follow-up with significant impact on patient survival [96]. Beside the well-known PRES, calcineurin inhibitors may cause a reversible cerebral vasoconstriction syndrome that can progress to cerebral infarction [97]. Furthermore neurovascular complication – including stroke and transient ischemic attacks (TIA) – occur commonly upon initial presentation of thrombotic microangiopathies presentation and cryptogenic stroke may develop before the onset of alarming hematologic abnormalities [98, 99].

Screening and preventive recommendations

The risk of a first stroke can be assessed by a global risk assessment tool such as the American Heart Association/American College of Cardiology Cardiovascular Risk Calculation online tool for adults (http://my.americanheart.org/cvriskcalculator), which has also been endorsed by the American Academy of Neurology [100]. The USPSTF recommends against screening for asymptomatic carotid artery stenosis in the general adult population. Preventive practice includes performing moderate to vigorous aerobic physical activity for at least 40 minutes 3-4 times a week, statin therapy according to 10 year calculated cardiovascular risk, implementation of a Mediterranean diet, HTN therapy, and weight loss in overweight and obese patients. Current guidelines for HCT recipients do not provide specific screening recommendations for stroke [14]. In the absence of HCT-specific evidence, these goals represent appropriate guidelines for HCT recipients.

Recommendations for screening and preventive practices

While evidence demonstrating the benefits of screening and preventive practices in HCT survivors is lacking, this review of MetS and cardiovascular disease emphasizes the high incidence of cardiovascular risk factors and the related morbidity and mortality experienced by HCT recipients. Based on this data, we present published guidelines for general population and HCT survivors as well as consensus recommendations on the screening (**Table 2**) and preventive practices (**Tables 3**) for MetS and cardiovascular disease. HCT survivors with no identifiable risk factors should be counseled to have a healthy lifestyle and to

follow the well-established screening recommendations for the healthy population. However, high-risk patients with ongoing risk factors should be more closely monitored.

Although not addressed formally in this manuscript, endocrine abnormalities, such as male hypogonadism, premature menopause, and hypothyroidism can occur following HCT and may contribute to MetS cardiovascular risk. Health care providers should be aware of these risks and evaluate for these conditions in HCT survivors, especially in the presence of MetS or those with risk factors.

A number of online tools are available to help providers assess risk in patients. In addition to the Framingham risk score (http://cvdrisk.nhlbi.nih.gov), the AHA released a mobile application in 2013 (http://tools.acc.org/ASCVD-Risk-Estimator) to estimate 10-year and lifetime risks for atherosclerotic cardiovascular disease in healthy subjects considering age, ethnicity, gender, systolic BP, history of smoking and DM, total and HDL cholesterol. However, it is important to acknowledge that these tools have not been validated in HCT survivors and thus potentially underestimate risk in this population.

Conclusion

We provide a consensus recommendations for screening and preventive measures for MetS and cardiovascular disease in recipients of HCT. Such effort by the CIBMTR and EBMT Late Effects Working Groups is intended to raise awareness of the cardiovascular risk in HCT survivors and lead to practices that will decrease related mortality. This document does not discuss strategies to achieve these practices (e.g. survivorship clinics, rehabilitation or exercise programs) given the differences in health care environments between different countries, but efforts to facilitate such strategies to be developed at the local or national level are needed.

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Table 1. Definitions of metabolic syndrome according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATPIII), the International Diabetes Federation (IDF), the American Heart Association (AHA), and the World Health Organization (WHO).

Table 2. Screening guidelines for metabolic syndrome and cardiovascular risk factors for adult and pediatric patients amongst the general population and HCT survivors

Table 3. Preventive practice recommendations for metabolic syndrome and cardiovascular risk factors for adult and pediatric patients amongst the general population and HCT survivors