Biol Blood Marrow Transplant 25 (2019) e310–e316

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Early Prediction of Cardiovascular Risk after Hematopoietic Cell Transplantation: Are We There Yet?

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Article history:
Received 9 May 2019
Accepted 10 July 2019

Keywords:
Cardiovascular risk
Subclinical target organ damage
Endothelial dysfunction
Hematopoietic cell transplantation

A B S T R A C T

Cardiovascular (CV) events have emerged as a major cause of morbidity and mortality among hematopoietic cell transplantation (HCT) survivors. Accumulating evidence supports the presence of increased CV risk in HCT recipients. Most studies have focused mainly on traditional CV risk factors, such as the metabolic syndrome and hypertension. However, detection of these factors suggests the development of irreversible overt clinical atherosclerosis. Therefore, earlier prediction of CV risk is needed to prevent CV morbidity and mortality in these patients. In the field of CV research, endothelial dysfunction is considered an early event in the pathophysiology of CV risk factors, and a number of markers have been proposed for its assessment. In addition, markers of subclinical target organ damage have been introduced to implement CV risk prediction and early preventive or intensive therapeutic interventions. Furthermore, a number of CV models have been suggested aiming for optimal stratification of patients. Preliminary studies have indicated excess CV risk using these early markers in HCT recipients. However, their role in the pathophysiology and clinical practice in HCT survivors remains largely understudied. Taking into account the need for increased awareness from treating physicians in this evolving setting, we conducted a state-of-the-art review aiming to summarize current knowledge on endothelial dysfunction, subclinical target organ damage, and CV risk prediction in HCT survivors.

INTRODUCTION

Hematopoietic cell transplantation (HCT) is the only curative option for a plethora of hematologic malignant and non-malignant diseases, as well as immunologic disorders [1]. Despite significant advances in the standard of care [2], cardiovascular (CV) events have emerged as a major cause of morbidity and mortality among HCT survivors without relapse or secondary malignancy, only second to the severe complication of graft-versus-host disease (GVHD) [3,4]. As a result, CV mortality is 2- to 4-fold higher than that of the general population, increasing with time from HCT [5].

Although this is a relatively new field of study, accumulating evidence supports the presence of increased CV risk in HCT recipients [6]. Interestingly, HCT survivors are not at higher risk of heart failure compared with their siblings, indicating that different mechanisms are responsible for the increased CV risk [7,8]. A number of recent studies have addressed this issue focusing mainly on traditional CV risk factors, such as the metabolic syndrome [9] and hypertension [10]. In addition, specific guidelines have been issued for management of CV risk factors in HCT recipients [11,12]. It should be noted, however, that detection of these factors suggests the development of irreversible overt clinical atherosclerosis. Therefore, earlier prediction of CV risk is needed to prevent CV morbidity and mortality in these patients.

In the field of CV research, endothelial dysfunction is considered an early event in the pathophysiology of CV risk factors, and a number of markers have been proposed for its assessment [13]. In addition, markers of subclinical target organ damage have been introduced to implement CV risk prediction and early preventive or intensive therapeutic interventions [14]. Last, CV risk prediction has a prominent role. A number of CV models have been suggested aiming for optimal stratification of patients into low, intermediate, or high CV risk in different clinical settings [15]. Despite advances in this field, only a few studies have implemented tools of early CV risk prediction in patients with HCT [16–21]. Therefore, their role in the pathophysiology and clinical practice in HCT survivors remains largely understudied.

Taking into account the need for increased awareness from treating physicians in this evolving setting, we conducted a

Financial disclosure: See Acknowledgments on page 314.

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https://doi.org/10.1016/j.bbmt.2019.07.012
1083-8791/

state-of-the-art review aiming to summarize current knowledge on CV risk prediction, subclinical target organ damage, and endothelial dysfunction in HCT survivors.

ENDOTHELIAL DYSFUNCTION

Over the past decades, our understanding of endothelial dysfunction has changed dramatically. Endothelial dysfunction contributes to subclinical target organ damage and triggers the development of atherosclerosis within the vascular walls as an early event in the pathophysiology of CV disease [13]. Endothelial dysfunction is characterized by impaired arterial dilation in response to biological and mechanical stimuli. Decreased bioavailability within the vasculature of the potent vasodilator nitric oxide, owing to either impaired synthesis or excessive oxidative degradation, is considered the cornerstone of endothelial dysfunction [22,23].

Invasive methods were used to measure endothelial dysfunction [24] until 1992, when Celermajer et al. [25] described the first noninvasive endothelial function test. Since then, a number of markers have been suggested for the estimation of endothelial dysfunction. Table 1 summarizes proposed markers of endothelial dysfunction, depending on either the measurement of circulating molecules or the functional evaluation with vascular methods.

Asymmetric dimethylarginine (ADMA), oxidized low-density lipoprotein, endothelial microvesicles (EMVs), endothelial progenitor cells, and endothelial glycocalyx have been investigated as novel biomarkers of endothelial dysfunction [26]. ADMA, an endogenous inhibitor of endothelial nitric oxide synthase, has been widely studied as a molecule reflecting endothelial dysfunction in CV diseases and essential hypertension [23,27]. A recent meta-analysis showed that elevated levels of circulating dimethylarginines are independent risk markers for all-cause mortality and CV disease across different populations and methodologic approaches [28]. ADMA has also shown associations with vascular markers of endothelial dysfunction (ie, forearm blood flow [29] and flow-mediated dilatation [FMD] [30]). Another biomarker of endothelial dysfunction that has gained increasing attention are EMVs. EMVs are vesicles shed from endothelial cell membranes carrying endothelial proteins as a result of cellular activation or apoptosis [31]. EMVs display important and multiple biologic properties that implicate them in several pathophysiologic pathways, including the pathogenesis of CV diseases. Detection of circulating EMVs by flow cytometry has been reported to be elevated in patients with a variety of CV comorbidities, including diabetes, hypertension, acute coronary syndromes, and chronic ischemic heart disease [32].

Table 1
Markers of Endothelial Dysfunction

Method	Marker
Functional evaluation with vascular tests	Forearm blood flow
	Flow-mediated dilation
	Peripheral arterial tonometry
	Laser Doppler flowmetry
Measurement of circulating biomarkers	Asymmetric dimethylarginine
	Oxidized low-density lipoprotein
	Endothelial microvesicles
	Circulating endothelial cells
	Endothelial progenitors
	Endothelial glycocalyx

Vascular markers of endothelial dysfunction include invasive measurement of forearm blood flow by venous occlusion plethysmography and the more recently developed noninvasive FMD, peripheral arterial tonometry, and laser Doppler flowmetry [26]. FMD is considered the most reproducible, predictive, inexpensive, and low-risk noninvasive method of endothelial function evaluation [33]. It estimates endothelium-dependent dilation in response to shear stress. FMD has been found impaired in patients with traditional CV risk factors [34–37] and CV disease [25]. FMD also predicts CV events and mortality in various clinical settings [38–40].

In HCT survivors, indices of endothelial dysfunction have only recently been evaluated, and available data are limited [18,19,21]. Poreba et al. [21] found significantly impaired FMD after autologous and allogeneic HCT. Administration of fludarabine and cytarabine, as well as increased creatinine, was associated with impaired FMD [21]. However, in studies of HCT recipients compared with controls, no difference in FMD was observed [18,19]. The latter study by Vatanen et al. [18] was limited by the relatively low number of participants, whereas the study by Dengel et al. [19] used siblings of HCT recipients as controls. Safe conclusions will only be made when an adequate number of patients based on power calculations are compared with control individuals who have not undergone HCT, matched for traditional CV risk factors in a 1:1 ratio. Table 3 summarizes available studies.

Among biomarkers of endothelial dysfunction, circulating endothelial cells and EMVs have been measured in HCT recipients. EMVs were found significantly increased in the early post-transplant period (2 to 3 weeks post-transplantation) [41] and in patients with acute GVHD [42]. EMVs have also been implicated in the pathophysiology of acute GVHD by a recent experimental study [43]. In addition, circulating endothelial cells have been studied as markers of endothelial dysfunction in HCT recipients [44,45]. However, it should be noted that none of the abovementioned studies has investigated a link between endothelial dysfunction and CV risk in HCT recipients.

SUBCLINICAL TARGET ORGAN DAMAGE

Accumulating evidence supports that subclinical alterations observed after HCT may significantly contribute to the premature onset of an impaired cardiometabolic phenotype and the accumulation of CV risk factors, such as hypertension, obesity, and diabetes mellitus, subsequently leading to established CV disease in HCT recipients [15]. Estimation of subclinical target organ damage is nowadays considered necessary in CV risk prediction because it adds significant information in terms of CV risk stratification beyond traditional CV risk factors [14]. Table 2 summarizes established markers of subclinical target organ damage.

The only study that has systematically assessed all markers of subclinical target organ damage in HCT recipients has enrolled 64 children at approximately 3 years after allogeneic HCT, showing a surprisingly high rate of subclinical CV organ damage and classical risk factors [16]. Table 3 summarizes studies evaluating subclinical cardiac and extracardiac organ damage in HCT recipients. Arterial stiffness and subclinical atherosclerosis will be further analyzed in different subparagraphs.

Although peripheral arterial disease has been considered a CV event in HCT recipients [46], measurement of the ankle-brachial index has not been reported in this population. Similarly, ischemic microvascular retinopathy has been recognized as a non-GVHD ocular complication in HCT recipients that needs to be prevented by treating CV risk factors [47]. However,

Table 2
Established Markers of Subclinical Target Organ Damage

Target Organ Damage	Marker	Method	Values or Signs Indicative of Target Organ Damage
Arterial stiffness	PWV	Applanation tonometry	>10 m/s
	Pulse pressure	Applanation tonometry	≥60 mm Hg
Subclinical atherosclerosis	Carotid IMT	Carotid ultrasound	≥0.9 mm or presence of atherosclerotic plaques
LVH	LVH	ECG	Sokolow-Lyon index >35 mm, R in aVL >11 mm; Cornell voltage duration product >2440 mm.ms, Cornell voltage >28 mm in men or >20 mm in women
	LV mass	Cardiac ultrasound	LV mass index: men >50 g/m; women >47 g/m
Microalbuminuria	Albumin	24-hour urine	30-300 mg/24 h
	Albumin-creatinine ratio	Morning spot urine	30-300 mg/g
Moderate CKD	eGFR	Equations	>30-59 mL/min/1.73 m^2
Severe CKD	eGFR	Equations	<30 mL/min/1.73 m^2
Peripheral artery disease	Ankle-brachial index	Doppler ultrasound	<0.9
Advanced retinopathy	Retinal alterations	Fundoscopy	Hemorrhages or exudates, papilloedema

LVH indicates left ventricular hypertrophy; ECG, electrocardiogram; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

earlier markers of retinal vascular changes with a prognostic value for future CV disease have not been studied [48–51].

Microalbuminuria and left ventricular (LV) mass indicating LV hypertrophy may be easier to access in the clinical setting. Nevertheless, only a few studies have assessed them in HCT recipients. Despite kidney damage being common in HCT recipients due to multiple triggers [52], the presence of microalbuminuria has been seldom reported. Microalbuminuria was common in previously irradiated patients [53], as well as patients with metabolic syndrome [54] and GVHD [55]. In the pediatric population, microalbuminuria and LV hypertrophy were found in 11% of the patients [16]. LV mass has also been found increased in patients with GVHD [56,57] and patients who had previously received cyclophosphamide [58]. No difference in LV mass between 16 pediatric HCT recipients and 16 controls was found in the only case-control study available [17]. This study is limited by a rather small study population [17].

ARTERIAL STIFFNESS

Increased arterial stiffness mainly results from progressive elastic fiber degeneration in the medial layer of the aorta and other major arteries, secondary to aging and the accumulation of traditional CV risk factors. It is an integral part of the physiology of aging and the pathophysiology of CV diseases [59,60]. Humoral factors, such as activation of the renin-angiotensin-aldosterone system, are also implicated [61]. The noninvasive measurement of pulse-wave velocity (PWV) is considered the most robust marker of arterial stiffness and is widely used to estimate vascular dysfunction. It is calculated by applanation tonometry recording the carotid and femoral pulse-wave forms. Using the same devices, central hemodynamic indices can be measured: central (aortic) blood pressure and augmentation index, a measure of enhanced arterial wave reflection [62]. PWV and central hemodynamics are strong and well-established predictors of CV risk and all-cause mortality [63,64]. As a result, PWV is recommended by current guidelines as part of the clinical evaluation of hypertensive patients [14]. Arterial stiffness indices are currently estimated not only in hypertensive individuals [65–67] but also intensively in other groups of patients with increased CV risk [68,69].

In HCT recipients, PWV has been measured only in patients who underwent transplantation during childhood. It was

Table 3
Studies Evaluating Subclinical Cardiac and Extracardiac Organ Damage in HCT Recipients

First Author	Year	Population	HCT Type	Marker	Result
Paiman [17]	2019	16 young adults, 16 controls	Pediatric allogeneic and autologous	PWV, LV mass	No difference
Borchert-Mörlins [16]	2018	64 children	Pediatric allogeneic	PWV, LVMI, IMT	Increased in 6% (PWV), 11% (LVMI), 48% (IMT) of patients
Dengel [19]	2019	108 young adults, 83 siblings	Allogeneic and autologous HCT at ≤21 years	cSD, DD, cLD, IMT, FMD	Increased, except for IMT and FMD
Vatanen [20]	2017	19 adolescents and young adults	Pediatric allogeneic or autologous HCT	CACOMP, IMT	Associated with hsCRP
Poreba [21]	2016	43 adults	Adult allogeneic or autologous HCT	BAD, FMD	Impaired after HCT
Vatanen [18]	2015	19 adolescents and young adults, 20 controls	Pediatric allogeneic or autologous HCT	FALDD, BALDD, RALDD, CACOMP, CASTIF, IMT, brachial diameter, FMD	Increased, except for FMD
Hingorani [55]	2015	65 adults and children	Pediatric and adult allogeneic HCT	Microalbuminuria	Increased incidence of acute GVHD
Majhail [54]	2009	86 adults and 258 controls	Allogeneic HCT	Microalbuminuria	Increased
Socie [102]	2001	105 adults	Allogeneic HCT	Microalbuminuria	More frequent in irradiated patients

LVMI indicates left ventricular mass index; CACOMP, common carotid artery compliance; hsCRP, high-sensitivity C-reactive protein; BAD, brachial artery diameter; FALDD, femoral artery lumen diameter in end-diastole; BALDD, brachial artery lumen diameter in end-diastole; CASTIF, common carotid artery stiffness index.

found increased in 6% of allogeneic HCT recipients [16]. Nevertheless, compared with controls, another study enrolling mainly allogeneic HCT recipients found no significant difference in PWV values [17]. Other markers of arterial stiffness in the carotid artery have also been impaired in case-control studies in the transplant setting. Indeed, carotid stiffness was increased in 19 autologous HCT recipients compared with controls [18]. In a larger study of allogeneic and autologous HCT recipients and controls, carotid cross-sectional distensibility and diameter compliance were lower only in irradiated HCT recipients compared with their siblings [19]. However, these markers are not easily comparable among studies and not widely used like PWV. Relevant studies are summarized in Table 3.

SUBCLINICAL ATHEROSCLEROSIS

Vascular atherosclerosis plays a critical role in the development and progression of CV disease. Subclinical atherosclerosis precedes irreversible CV disease and remains clinically silent for years or even decades, until it manifests clinically as CV events. Early identification of increased subclinical atherosclerotic burden is critical as an alarming sign prompting CV disease prevention strategies and more aggressive treatment of predisposing factors [14].

Carotid intima media thickness (IMT) represents a well-established method for the assessment of macrovascular structure and a robust, most widely applied marker of subclinical atherosclerosis. It reliably reflects the total atheromatous burden of the arterial system [70,71]. IMT is measured noninvasively by ultrasound examination according to consensus guidelines [72]. Furthermore, it has been associated with traditional CV risk factors, including age, sex, smoking, obesity, hypertension, and dyslipidemia [73–77]. Last, IMT strongly predicts CV events not only in patients with CV comorbidities [78] but also in healthy individuals [79].

In pediatric autologous HCT, increased IMT has been independently associated with increased inflammatory markers, suggesting that these patients may be more prone to early vascular aging [20]. Increased IMT has also been found in a previous case-control study of the same group, suggesting that patients irradiated with total-body irradiation in childhood presented with early arterial aging as young adolescents and adults [18]. In the allogeneic setting, 48% of pediatric HCT recipients have shown IMT values above the 95th percentile [16]. Nevertheless, in a case-control study of 108 HCT recipients, IMT was not increased compared with their siblings [19]. Limitations regarding the control group that have been mentioned above do not allow for safe conclusions from available data. Table 3 summarizes relevant studies.

CARDIOVASCULAR RISK PREDICTION MODELS

The increasing number of HCT survivors soon unmasked the acute and delayed CV toxicity related to the primary disease and the applied therapeutics. CV alterations induced by chemotherapeutic agents include arrhythmias, especially bradycardia and QT interval prolongation, myocardial ischemia or infarction, left ventricular dysfunction, and hypertension [80]. A number of studies have documented an increase in supraventricular tachyarrhythmia after HCT [81]. Atrial fibrillation has been reported as a major cardiac complication primarily in the autologous rather than the allogeneic HCT setting, with an incidence of 7% to 27% [82–84].

Acute and chronic CV adverse effects have a major impact on the quality of life of HCT patients responding to treatment and may significantly decrease life expectancy, either directly or by limiting future treatment options. Indeed, CV mortality represents a leading cause of death in long-term survivors of HCT who do not relapse and stay free from secondary malignancies [3,4]. Allogeneic HCT survivors seem to experience more premature CV events compared with autologous HCT patients [46]. In this context, it is imperative to introduce CV risk prediction models that can effectively and accurately predict future CV risk in this particular group of patients.

Several models have been developed for the prediction of incident CV disease in the general population, which mathematically combine multiple predictors to calculate future risk of CV disease, typically a common set of traditional CV risk factors such as age, sex, blood pressure, smoking, diabetes, and cholesterol levels. The most widely applied are the Framingham [85–87], Systematic COronary Risk Evaluation (SCORE) [88], and QRISK [89–91] models. Clinical guidelines have embedded some of these prediction models in their proposed therapeutic algorithms [14,92]. In several countries, CV risk prediction models have been incorporated in electronic health platforms to calculate 10-year risk of CV disease and affect decision making for several groups of patients with high CV risk such as those with hypertension, diabetes, and established CV disease. However, most of the models have not been externally validated, with the exception of the most commonly used, such as the Framingham and SCORE models [93]. Most important, when it comes to specific populations and clinical settings, including HCT recipients, health policy makers are still confused on which prediction model to advocate.

HCT survivors are characterized by an increased prevalence of traditional CV risk factors included in traditional CV risk prediction models [5,94]. However, results from these studies have been conflicting in terms of the role of transplant-associated factors. Some studies have indeed reported associations between transplant-associated factors and traditional CV risk factors [5,94]. By contrast, such associations were not confirmed by others [46,54,95]. The global CV risk score has been previously used to express increased CV risk in HCT recipients [95]. The Framingham general CV risk score has also shown increased CV risk in male survivors [96]. Interestingly, diabetes and CV comorbidity as derived by the HCT comorbidity index independently predicted nonrelapse mortality in a recent study [97].

Novel HCT-specific CV risk prediction models have been proposed to promote the timely identification of high-risk individuals and the development of targeted diagnostic and therapeutic approaches toward CV risk reduction after HCT [98]. However, such an effort is challenging and requires validation of the models under construction and head-to-head comparisons with the existing models for the general population in the setting of large prospective studies. For instance, several CV risk algorithms have developed over the past years specifically for patients with rheumatoid arthritis, an autoimmune chronic inflammatory disease characterized by excess CV morbidity and mortality [15]. These models presumably improved diagnostic accuracy by taking into account both traditional CV risk factors and disease-related characteristics. However, when they were compared with the general population CV risk calculators, including Framingham Risk Score, they did not seem to predict CV risk more accurately, thus raising reasonable doubts about their clinical utility [99].

Considering the increased CV mortality and morbidity in HCT recipients and the lack of available data, future studies should focus on tailoring the existing models to this particular group of patients and aim at the improvement of their predictive performance by the addition of novel predictors. Interestingly, experimental studies have suggested that the donor's CV

Table 4
Recommendations for Clinical Practice and Research in Early Cardiovascular Risk Prediction after HCT

Clinical Practice	Clinical Research
Predict cardiovascular risk using existing prediction models	Assess which cardiovascular risk prediction model is suitable for HCT recipients
Monitor and manage traditional modifiable cardiovascular risk factors (hypertension, dyslipidemia, diabetes, obesity)	Determine transplant- or patient-related factors associated with traditional cardiovascular risk factors and established markers of subclinical target organ damage
Assess established markers of subclinical target organ damage	Investigate which markers of subclinical target organ damage can be used as early markers of cardiovascular risk prediction in well-designed prospective studies
Collaborate with internists and cardiologists in long-term follow-up clinics	Elucidate the pathophysiology of increased cardiovascular risk (ie, endothelial dysfunction)

risk factors may alter the CV profile of HCT recipients [100]. This observation indicates that CV risk prediction models may be useful not only for HCT recipients but also for donor selection. However, this hypothesis remains to be further studied in the clinical setting.

CONCLUSIONS AND FUTURE PERSPECTIVES

In conclusion, early detection of CV risk is feasible in HCT recipients using a number of novel available markers. Heterogeneous studies in rather small populations have been performed so far, mostly in the pediatric setting. Our review highlights the lack of relevant research in this field, which might be in part attributed to multiple other complications studied in these patients. Future studies are needed to recognize the most robust panel of markers to be used in clinical practice and their prognostic value in this specific group of patients. Table 4 summarizes recommendations for clinical practice and research in this field. Given the heterogeneity of long-term follow-up care [101], long-term efforts are warranted to incorporate CV risk prediction in everyday clinical practice by a multidisciplinary approach involving teamwork by hematologists, internists, and cardiologists.

ACKNOWLEDGMENTS

Financial disclosure: The authors have nothing to disclose.

Conflict of interest statement: There are no conflicts of interest to report.

Authorship statement: E. Gavriilaki contributed to study concepts, design, and writing of original draft. E. Gkaliagkousi contributed to data analysis and interpretation, as well as writing of the original draft. I.S. and P.A. contributed to data acquisition and quality control of data. S.D. and A.A. reviewed and edited the final manuscript.

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