Late cardiovascular events after allogeneic hematopoietic stem cell transplantation: a retrospective multicenter study of the Late Effects Working Party of the European Group for Blood and Marrow Transplantation

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ABSTRACT

Background

Long-term outcome after hematopoietic stem cell transplantation including late transplant-related events is of increasing interest. The aim of this study was to evaluate the incidence of cardiovascular events after allogeneic HSCT and to search for their risk factors.

Design and Methods

This is a retrospective mutlicenter European Group of Blood and Marrow Transplantation (EBMT) analysis, including 548 long-term survivors treated in ten EBMT transplant centers, who underwent hematopoietic stem cell transplantation between 1990 and 1995 and survived ≥1 year after the transplant. All arterial events occurring after hematopoietic stem cell transplantation (cerebral, coronary, peripheral) were reported.

Results

Twenty (3.6%) out of 548 patients had a cardiovascular event in at least one arterial territory. The median age at occurence of cardiovascular events was 54 years (range, 41-70). The cumulative incidence of a first arterial event 15 years after hematopoietic stem cell transplantation was 6% (95% CI, 3%-10%). The cumulative incidence for patients with a high global cardiovascular risk score, defined as having ≥50% of the risk factors (arterial hypertension, diabetes, dyslipidemia, increased body-mass index, physical inactivity, smoking) was 17%, as compared to 4% in those with a low risk score. In multivariate analysis age older than 30 years at last follow-up, and a high global cardiovascular risk score were associated with, respectively, 6.4-fold and 9.8-fold increases in the risk of an arterial event.

Conclusions

Long-term survivors after allogeneic hematopoietic stem cell transplantation are likely to have an increased risk of premature cardiovascular accidents.

Key words: stem cell transplantation, cardiovascular, late effects, long-term survivors.

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Introduction

Allogeneic hematopoietic stem cell transplantation (HSCT) is the treatment of choice for defined malignant and non-malignant hematologic disorders.[1] With the constant improvement of the outcome over the last decades, and the increased number of transplanted patients, general health status in long-term survivors and the development of late events related to HSCT have gained increasing interest.[2-5] HSCT remains associated with considerable late morbidity and mortality. 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. Secondary tumors, cataract development, pulmonary complications, and infertility or endocrine dysfunctions are some of the late complications that have been well described.[6-10] For other organ dysfunctions or complications, particularly when occurring with a low frequency after HSCT, an unequivocal relationship with the transplant procedure is more difficult to demonstrate. Cardiovascular events after allogeneic HSCT could fall into such a category. Reasons for low reporting can be the long time interval needed for a clinical manifestation to occur. Indeed, cardiovascular accidents would be expected decades after transplantation.

Atherosclerosis is now considered as an inflammatory process in which endothelial lesions occur decades before clinical manifestations.[11-13] Common risk factors for atherosclerosis are well established in the general population.[14] They include smoking, arterial hypertension, obesity, diabetes, dyslipidemia and physical inactivity. In patients who have undergone allogeneic HSCT, additional transplant-related factors such as total body irradiation (TBI) or graft-versus-host disease (GvHD) could play a role. Indeed, endothelial damage is induced by the conditioning regimen with or without TBI.[15,16] Furthermore, vascular endothelial cells have been documented to be a target of GvHD.[17] Increased cardiovascular risk factors, such as impaired glucose tolerance or dyslipidemia as late effects after HSCT could be the result of post-transplant endocrine dysfunction, prolonged treatment with immunosuppressive drugs, or a sedentary life-style after HSCT.[18]

There have been anecdotal case reports on arterial complications, most of them with a dramatic course, observed in unexpectedly young patients.[19-25] Recently, two studies on cardiovascular risk factors and the risk of cardiovascular disease in long-term survivors after HSCT have been published. First, a large collaborative cohort study from the United States showed that survivors after allogeneic HSCT have a higher age- and body mass index (BMI-)adjusted risk of diabetes and hypertension, potentially leading to a higher than expected risk of cardiovascular events according to age.[26] Second, a single center retrospective study showed that the cumulative incidence of late vascular events was significantly higher after allogeneic HSCT than after autologous HSCT.[27] The aim of this study was to evaluate the prevalence and risk factors of arterial complications occurring in patients who survived al least 1 year after allogeneic HSCT.

Table 1. Type of cardiovascular events for which the questionnaire collected information.

Cerebrovascular events
Stroke
Transient ischemic attack
Lacunar defect
Patients who had received any kind of revascularization therapy in relation to atherosclerosis
Coronary artery disease
Angina pectoris
Myocardial infarction
Chronic coronary heart disease
Patients who had received any kind of revascularization therapy in relation to atherosclerosis
Peripheral artery disease
Claudication
Rest pain
Acute ischemia
Gangrene
Patients who had received any kind of revascularization therapy in relation to atherosclerosis
Patients who had had a limb amputated in relation to atherosclerosis

Asymptomatic manifestations, such as arterial bruits, were not taken into consideration.

Design and Methods

This was a retrospective multicenter study of the Late Effects Working Party of the European Group of Blood and Marrow Transplantation (EBMT). Participating centers agreed to review charts and to report events and risk factors in all consecutive patients eligible for the study (subjects who had undergone allogeneic HSCT between 1990 and 1995, and who survived for at least 1 year after the transplant). In order to ensure completeness of the reporting, the EBMT Central Office sent a labeled questionnaire for each individual patient registered and fulfilling the inclusion criteria to all participating centers. Return of questionnaires was controlled centrally. Individual patients were not contacted. We analyzed the type and prevalence of arterial events in patients without pre-existing arterial disease, as well as risk factors for atherosclerosis. Any type of arterial vascular event, cerebrovascular, cardiovascular, or peripheral arterial disease, was considered for the purpose of this study. For each patient demographic data, disease and disease state, the use of TBI as conditioning regimen, the occurrence of acute and chronic GvHD, and survival status were recorded. The time intervals between first transplantation and last follow-up, first arterial vascular event, and/or death were documented.

A cerebrovascular event was retained for analysis when a stroke, transient ischemic attack, cerebral arterial occlusion, or lacunar infarct was reported. Coronary heart disease was defined as angina pectoris, myocardial infarction, or chronic coronary heart disease. A

peripheral arterial event was retained for analysis in the case of claudication, rest pain, acute ischemia, or gangrene (Table 1). The following risk factors for the development of arterial events were assessed: sex of the patient, age at transplantation and at first vascular event or last follow-up, disease and stage of the disease, TBI used for conditioning, and occurrence and degree of acute and chronic GvHD. Additionally, some of the established cardiovascular risk factors such as arterial hypertension, diabetes mellitus, dyslipidemia, increased BMI, smoking habits since HSCT and physical inactivity at the time of last follow-up were included. Diabetes was retained for patients requiring anti-diabetic therapy. Dyslipidemia was defined as increased plasma lipids (total cholesterol or LDL cholesterol or triglycerides), or when patients were receiving cholesterol-lowering therapy. We classified a patient as overweight when the person's BMI was greater than 25 kg/m^2.

For the multivariate analysis and determination of the cumulative incidence of cardiovascular risk factors, a global cardiovascular score, including all available data on risk factors for each patient, was constructed. Thus, we added up all risk factors (arterial hypertension, dyslipidemia, diabetes, being overweight, smoking, physical inactivity), attributing one point to each of them. When information on a specific risk factor was not available, no point was attributed, therefore counting this as absence of the risk factor. We used a similar weighting for each risk factor (one point each). The global cardiovascular risk score was expressed as a percentage of positive risk factors, after exclusion of the absent factors. GvHD and age were not included in this risk score. The median number of risk factors for which information was available was five (out of six) per patient. For 74 of the 548 (13%) patients the global risk score could not be calculated because of complete absence of information or because information on only one risk factor was available. For the multivariate analysis a global cardiovascular risk score of ≥50% was considered as positive, since a cut-off of 50% allowed a good discrimination in the cumulative incidence analysis.

Patients' characteristics

Ten centers reported on 548 patients who were transplanted between 1990 and 1995 and survived 1 year or more after allogeneic HSCT. The participating centers and the number of patients provided by each center are listed in the Appendix. The characteristics of the patients are shown in Table 2. There were 312 (57%) males and 236 (43%) females. The median age at HSCT was 27 years (range, 0.5-59) and that at last follow-up 35 years (range, 3-72). The median time between transplantation and last follow-up or first arterial event was 9 years (range, 1-16). Four hundred and sixty-seven patients (85%) were transplanted for a hematologic malignancy and 81 (15%) for a non-malignant disease (aplastic anemia, hemoglobinopathy, immune deficiencies, other inborn errors). TBI was used for conditioning in 316 patients (58%). The proportion of patients in whom TBI was used for conditioning was high for lymphoid neoplasms (79%) and acute leukemia (72%), intermediate for myelodyplastic/myeloproliferative syndromes (56%), and chronic myeloid leukemia (56%), and low for non-malignant disorders (9%). Acute GvHD of any grade was observed in 355 patients (69%) patients, and chronic GvHD in 185 patients (34%). GvHD of any type (acute or chronic) and severity was observed in 289/548 (53%) patients.

Statistical analysis

Patients with and without an arterial vascular event following HSCT were compared, using the χ^2 test for categorical data and the Mann-Whitney U test for continuous variables. Variables included in the analysis were sex and age of the recipient, disease, stage of the disease, HLA match, TBI as conditioning regimen, acute and chronic GvHD, and duration of follow-up after HSCT. In addition to the patient- and transplantation specific-variables, common risk factors for atherosclerosis, such as physical inactivity, smoking, arterial hypertension, diabetes mellitus, dyslipidemia and BMI at the time of the last follow-up were included. The cumulative incidence of vascular complications was estimated with death without a vascular event being treated as the competing risk. Multivariate analysis of arterial events was performed with Cox regression analysis using the global risk score, and adding other variables in a backward stepwise manner. The incidence rate by age and sex is given as number of new events per 1,000 person-years. In all statistical procedures, $p<0.05$ was considered as the level of statistical significance. The statistical analyses were performed using SPSS statistical software (SPSS for Windows, Release 14.0, SPSS, Inc., Chicago, IL, USA), except for the cumulative risk analysis for which NCSS software, release March, 2004, was used.

Results

At the time of the last follow-up 422 of the 548 (77%) patients included in the long-term study and who had survived more than 1 year after allogeneic HSCT were alive. The probability of overall survival at 15 years after transplantation was 76% ± 3%. Twenty of the 548 (3.6%) patients had an arterial event in at least one territory. The median age at the time of the first arterial event was 54 years (range, 41-70); 18 had acute GvHD, and 10 had chronic GvHD. The median interval between the transplant and arterial event was 7 years (range, 1-13 years). The overall survival of the patients with an arterial event was 48% ± 21%, while it was 77% ± 3% for patients without an arterial event (p=0.27). In some of the patients an arterial event was reported in more than one territory. There were, therefore, a total of 29 types of arterial events reported in these 20 patients (9 cerebrovascular, 12 coronary artery, and 8 peripheral artery events). Fourteen patients had an arterial event in a single territory, three patients in two territories and three patients in all three arterial territories. In five patients the history obtained from the centers did not allow a firm conclusion to be drawn

with respect to the arterial event. These five patients were not, therefore, included in the group of patients with an arterial event. One had arterial fibrillation of unknown origin. A second patient had a sudden death of unknown cause (pulmonary embolism could not be ruled out). A third patient had a decreased left ventricular ejection faction of 35%. It was unclear whether this functional decrease was of toxic origin or related to chronic coronary disease. A fourth patient had a subarachnoidal bleed which resolved completely. The last of these five patients had a history of transient neurological symptoms that resolved completely and never reappeared. Initially the diagnosis of a transient ischemia attack was retained. However, we did not include this patient, since a cardiovascular event had never been proven.

Patients with an arterial event were significantly older at the time of transplantation (median age 44 versus 26 years; $p<0.001$), and at time of last follow-up or the first arterial event (median age 54 years versus 36

Table 2. Characteristics of all patients and statistical comparison between patients with and without arterial events.

Characteristics	*All patients*	*No arterial events*	*With arterial events*	*p value*
Number of patients	548	528 (96.4%)	20 (3.6%)	
Male gender, n (%)	312 (57%)	299 (57%)	13 (65%)	0.50
Median age at transplantation, (range) years	27 (0.5-59)	26 (0.5-58)	44 (29-59)	<0.001
Median age at last follow-up/at time of first event, (range) years	35 (3-72)	36 (3–72)	54 (41-70)	<0.001
Median follow-up time, (range) years	9 (1-16)	9.5 (1-16)	10 (2-15)	0.341
Number of patients alive at last follow-up, n (%)	422 (77%)	408 (77%)	14 (70%)	0.48
Primary disease				
Acute leukemia	257 (47%)	251 (47%)	6 (30%)	
Chronic myeloid leukemia	143 (26%)	137 (26%)	6 (30%)	
MDS/MPS	27 (5%)	23 (5%)	4 (20%)	0.001
Lymphoma, multiple myeloma	40 (7%)	36 (7%)	4 (20%)	
Non-malignant disorder	81 (15%)	81 (15%)	0	
Stage of the disease (n=489)				
Complete remission or chronic phase	372 (76%)	360 (77%)	12 (60%)	0.09
Any other more advanced stage	117 (24%)	109 (23%)	8 (40%)	
HLA match (n= 543)				
Identical sibling	455 (84%)	438 (84%)	17 (85%)	
Matched related or unrelated	68 (12.5%)	66 (12.5%)	2 (10%)	
Mismatched related or unrelated	17 (3%)	16 (3%)	1 (5%)	0.92
Syngeneic	3 (0.5%)	3 (0.5%)	0	
Total body irradiation used for conditioning	316 (58%)	302 (57%)	14 (70%)	0.28
Graft-versus-host disease (GvHD) (n=513)				
No acute GvHD	158 (31%)	156 (32%)	2 (10%)	
Acute GvHD grade 1-2	306 (59%)	289 (58%)	17 (85%)	0.039*
Acute GvHD grade 3-4	49 (10%)	48 (10%)	1 (5%)	
No chronic GvHD	363 (66%)	353 (67%)	10 (50%)	
Chronic GvHD	185 (34%)	175 (33%)	10 (50%)	0.118
Risk factors for atherosclerosis				
Regular physical activity (n=341)				
yes	187 (55%)	183 (56%)	4 (25%)	0.014
no	154 (45%)	142(44%)	12 (75%)	
Smoking habits (n=423)				
no	367 (87%)	357 (88%)	10 (59%%)	0.001
yes	56 (13%)	49 (12%)	7 (41%)	
Arterial hypertension (n=475)				
no	402 (85%)	396 (87%)	6 (30%)	<0.001
yes	73 (15%)	59 (13%)	14 (70%)	
Diabetes (n=475)				
no	444 (93%)	429 (94%)	15 (75%)	0.001
yes	31 (7%)	26 (6%)	5 (25%)	
Dyslipidemia (n=467)				
no	391 (84%)	383 (85%)	8 (42%)	<0.001
yes	76 (16%)	65 (15%)	11 (58%)	
Body mass index (n= 408)				
BMI ≤25	270 (66%)	262 (67%)	8 (44%)	0.044
BMI> 25	138 (34%)	128 (33%)	10 (56%)	

**Likelihood ratio (the others Pearson's χ^2). MDS: myelodysplastic syndrome; MPS: myeloproliferative syndrome.*

years; $p<0.001$). Patients with an arterial event more often had acute GvHD as compared to patients without an arterial event (90% with any grade of acute GvHD versus 68%; $p=0.039$) (Table 2). No difference was observed between the two groups of patients with regards to sex, median follow-up time since transplantation, TBI used for conditioning, stage of the disease, chronic GvHD and HLA matching ($p>0.05$). The type of the disease was related to the risk of an arterial event, although this is most likely due to certain disease types being associated with higher age such as myelodysplastic syndromes, myeloproliferative disorders and lymphoid neoplasia.

The questionnaire sent to the centers asked for information on the occurrence of established vascular risk factors at the time of the last follow-up. Overall physical inactivity was found in 45% of patients (154/341), persistent smoking in 13% (56/423), arterial hypertension in 15% (73/475), diabetes in 7% (31/475), dyslipidemia in 16% (76/467), and obesity with a BMI >25 kg/m^2 in 34% (138/408) (Table 2). In univariate analysis, all established risk factors for atherosclerosis were significantly more prevalent in patients with an arterial event. Patients with an arterial event after HSCT were more often sedentary (75% *vs.* 44%; $p=0.014$), more often persistent smokers (41% *vs.* 12%; $p=0.001$), more often had arterial hypertension (70% *vs.* 13%), diabetes (25% *vs.* 6%), and dyslipidemia (58% *vs.* 15%) and more often had a BMI >25 mg/m^2 (56% *vs.* 33%; $p=0.044$) as compared to patients without an arterial event.

The cumulative incidence of cardiovascular disease was 6% (95% CI, 3%-10%) at 15 years after HSCT (Figure 1). Patients with any of the established cardiovascular risk factors (smoking, physical inactivity, arterial hypertension, diabetes, dyslipidemia, increased BMI) had a significantly higher cumulative incidence of an arterial event (Table 3). The cumulative incidence of an arterial event at 15 years post-transplant for patients with a global risk score ≥50% was 17% (95% CI: 9-32%), as compared to a cumulative incidence of 4% (95% CI: 1-9%) in patients with a score below 50% (Figure 2). Patients with acute GvHD had a higher cumulative incidence of an arterial event (4%; CI 95%, 2-7%), as compared to patients without acute GvHD (1%; CI 95%; 0-4%; $p=0.022$). There was no difference in cumulative incidence of an arterial event depending on whether patients did or did not have chronic GvHD, or whether their conditioning regime included TBI (Table 3).

In multivariate Cox regression analysis older age at the time of transplantation (RR: 6.43; 95% CI, 1.87 to 22.06; $p=0.003$), and a high global cardiovascular risk score at the time of the last follow-up (RR: 9.81; 95% CI, 3.75 to 25.66; $p<0.001$) were statistically associated with an increased relative risk of an arterial vascular event after allogeneic HSCT (Table 4). Acute and

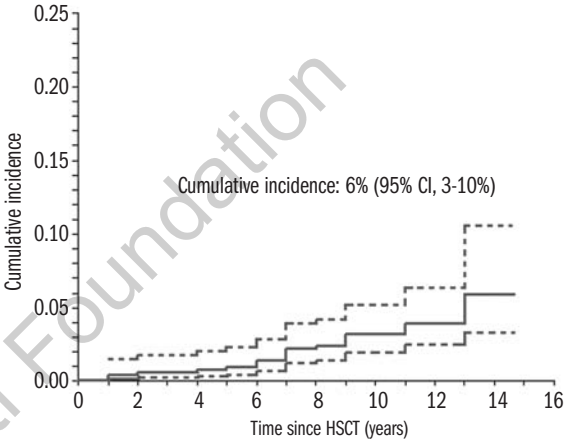

Figure 1. Cumulative incidence of late arterial events after allogeneic HSCT.

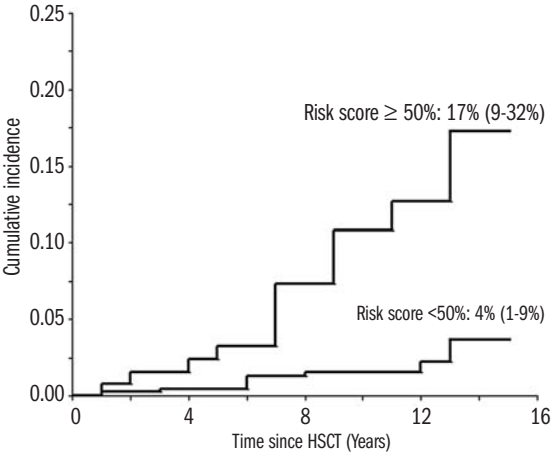

Figure 2. Cumulative incidence of arterial events according to the global cardiovascular risk score. The global cardiovascular score was constructed including all available risk factors known for each patient, (arterial hypertension, dyslipidemia, diabetes, smoking, and physical inactivity). A score of one point was given for each risk factor present. When information was not available, no point was given therefore counting this as absence of the risk factor. The global cardiovascular risk score was expressed as a percentage of positive risk factors, after exclusion of the absent factors. We compared here the patients with a global cardiovascular risk score of ≥50% to those with a risk score <50%.

Table 3. Cumulative incidence and 95% confidence interval of arterial after allogeneic hematopoietic stem cell transplantation in patients with and without risk factors.

Cumulative incidence of an arterial event at 15 years	*Without risk factor*	*With risk factor*	*p value*
Persisting smoking	3% (2-6%)	15% (7-30%)	0.0001
Physical inactivity	2% (1-6%)	7% (4-13%)	0.013
Arterial hypertension	2% (1-4%)	17% (12-26%)	0.0001
Diabetes mellitus	3% (2-5%)	10% (3-28%)	0.0001
Dyslipidemia	2% (1-4%)	12% (7-23)	0.0001
BMI > 25 kg/m^2	3% (1-6%)	7% (3-13%)	0.055
Acute GvHD	1% (0-4%)	4% (2-7%)	0.022
Chronic GvHD	2% (1-4%)	5% (2-10%)	0.185
Total body irradiation as conditioning	2% (1-6%)	4% (2-7%)	0.39

chronic GvHD, type of primary disease and stage of the disease were not significant once atherosclerotic risk factors and age had been adjusted for.

The incidence rate was 4.11 new cardiovascular events/1,000 person-years for the whole cohort, 4.89/1,000 person-years for men, and 3.17/1,000 person-years for women.

Discussion

In this retrospective multicenter study of the EBMT Late Effects Working Party, based on 548 long-term survivors treated with allogeneic HSCT between 1990 and 1995, 20 (3.6%) patients were reported to have had an arterial event. Some of these patients had an arterial event in more than one territory. Three patients had a cardiovascular accident in two territories, and three more patients in all three arterial territories. The cumulative incidence of an arterial event (cerebrovascular disease, coronary arterial disease and/or peripheral arterial disease) was 6% at 15 years. The cumulative incidence was 17% for patients with a high global cardiovascular risk score, as compared to 4% in the patients with a low risk score. In univariate analysis, but not in multivariate analysis, acute GvHD was associated with a higher risk of an arterial event after transplantation. In contrast, conditioning with TBI and chronic GvHD did not represent significant risk factors. In multivariate analysis, the relative risk of developing an arterial event after HSCT was increased 6-fold for patients older than 30 years at transplantation, and 9.5-fold for patients who had a high global cardiovascular risk score.

These results are in line with those presented by a recent single center study on late cardiovascular events in long-term HSCT survivors.[27] Likewise, we found an abnormally high number of cardiovascular events in any arterial territory affecting an unexpectedly young population of patients. In addition to the previously reported risk factors, which were older age and the established risk-factors, acute GvHD was associated with higher risk in the univariate analysis. Although the number of patients at risk was higher in the current study, we found a lower cumulative incidence of arterial events than that reported in the single center study: this could be explained by the shorter follow-up time of our study, and a possible data underestimation due to the multicenter character of this retrospective analysis.

We showed here that all established cardiovascular risk factors, taken individually, were more likely to be found in patients with an arterial event, as compared to in patients without such a complication. Patients with an arterial event after allogeneic HSCT had a higher probability of having arterial hypertension, diabetes mellitus, and dyslipidemia; they were more often sedentary and were more likely to smoke regularly. In multivariate analysis, the relative risk of a cardiovascular accident was 9.5 higher for patients with a high global cardiovascular risk score. It has been previously shown that hyperinsulinemia, impaired glucose tolerance, hypertriglyceridemia, low concentration of HDL cholesterol, and abdominal obesity are frequent after HSCT. These cardiovascular risk factors are more common among patients treated with allogeneic HSCT than among leukemia patients or healthy controls.[28] Dyslipidemia, glucose intolerance and arterial hypertension after allogeneic HSCT can be the consequence of prolonged, intensified immunosuppressive treatment[29] with cyclosporine, tacrolimus, sirolimus, mycophenolate and corticosteroids, or due to late organ effects after transplantation such as decreased growth hormone secretion in children, or hypothyroidism.

Table 4. Results of multivariate analysis of the risk factors for arterial complications.

Factor	*Relative Risk (OR)*	*95% confidence interval*	*p value*
Age at transplantation			
< 30 years	1	–	0.003
≥30 years	6.43	1.87-22.06	
Global cardiovascular risk score			
< 50%	1	–	<0.001
≥50%	9.81	3.75-25.66	

It has been demonstrated that the risk of a cardiovascular accident is increased in survivors of allogeneic HSCT.[27] The occurrence of vascular events at an earlier age than expected could not be explained solely by the established risk factors, such as hypertension, dyslipidemia or diabetes. As a possible explanation we add now, with caution, is the role of allogeneic attack to the endothelium in the setting of GvHD.[30] Endothelial GvHD could contribute to the endothelial injury responsible for atherosclerosis. Endothelial GvHD has been rarely described.[31-33] A loss of micro-vessels due to endothelial injury has been demonstrated in patients with chronic GvHD.[17,34] The fact that the risk of cardiovascular accidents is higher in patients treated with allogeneic than with autologous HSCT is a strong argument in favor of an immunological basis for these late events.[27] However, so far GvHD could not be demonstrated as a contributing risk factor for an arterial event.

Our study has a number of limitations, arising mainly from its retrospective character, the lack of a control population, as well as the possibility of not having picked up all the vascular events. Combining a heterogeneous group of complications as events of equal weight is another problematic issue. The questionnaire was designed to pick up all clinically relevant vascular events as well as cardiovascular risk factors. Demographic data, transplant- and disease- related data were obtained from the EBMT registry. Nevertheless, as this was an observational study, we cannot exclude that there was underreporting of vascular events and cardiovascular risk factors. We have no control group formed of a general matched population. However, the median age of onset of arterial events of 54 years in patients treated with allogeneic HSCT is much younger than that expected in the general popu-

lation. In a population-based Dutch study the median age at the time of a first cardiovascular event was 76 years.[35] Furthermore, the incidence rate of cardiovascular disease in our population is unexpectedly high. Indeed, the incidence rate is strongly correlated with age and sex. The risk increases with advancing age and is higher in males. There are only scarce data on the incidence of cardiovascular disease in people under 35 years of age. Recent epidemiological data show that the incidence rate in patients younger than 35 years is <1.0/1,000 person-years.[36] The median age of our cohort at the time of HSCT was 27 years. We can, therefore, conclude that with an incidence rate of 4.11 new events/1,000 person-years, it is likely that there is an excess of cardiovascular events in allogeneic HSCT recipients for any given age. Finally, *arterial vascular events* pools together disparate events. We focused our report on clinically evident vascular events of an atherosclerotic nature. We excluded all arterial events secondary to arterial embolism, acute infection or excessive thrombocytosis. Despite these limitations, this study, which, to our knowledge, is the largest report on cardiovascular events in long-term survivors after allogeneic HSCT, supports the hypothesis that cardiovascular events are increased after allogeneic HSCT.

In conclusion, compared to an age- and gender-matched population long-term survivors after allogeneic HSCT are likely to have an increased risk of premature cardiovascular events after transplantation, particularly when they present cardiovascular risk factors post-transplant. These data could be of particular importance for pre-transplant counseling of patients, and post-transplant follow-up of long-term survivors. The results presented here should draw attention to this potentially new late effect after allogeneic HSCT, and encourage transplant centers and primary care physicians to screen systematically for cardiovascular risk factors in long-term survivors after HSCT and, when necessary, institute appropriate treatment.

Appendix

List of the participating EBMT centers: Hôpital St. Louis, Paris, France, CIC 207 (227 patients included); University Hospital, Basel, Switzerland, CIC 202 (81 patients included); Hotel Dieu, Nantes, France, CIC 253 (74 patients included); St. Laszlo Hospital, Budapest, Hungary, CIC 556 (41 patients included); University Hospital Eppendorf, Hamburg, Germany, CIC 614 (34 patients included); University Hospital, Lund, Sweden, CIC 283 (28 patients included); Addenbrookes Hospital, Cambridge, UK, CIC 566 (22 patients included); Hôpital de Hautepierre. Strasbourg, France CIC n.a. (18 patients included); University Faculty of Medicine, Ankara, Turkey, CIC 617 (15 patients included); University Cattolica S. Cuore, Rome, Italy, CIC 307 (8 patients included).

Authorship and Disclosures

All authors participated in the analysis and interpretation of the data, revised the manuscript critically for intellectual content, and approved the final version to be published. JP, DW, AR and GS contributed to the conception and design of the study, and participated in drafting the article. The authors state that they have no potential conflicts of interest.

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