

REVIEW ARTICLE OPEN



Endothelial cell dysfunction: a key determinant for the outcome of allogeneic stem cell transplantation

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Allogeneic hematopoietic stem cell transplantation (alloSCT) carries the promise of cure for many malignant and non-malignant diseases of the lympho-hematopoietic system. Although outcome has improved considerably since the pioneering Seattle achievements more than 5 decades ago, non-relapse mortality (NRM) remains a major burden of alloSCT. There is increasing evidence that endothelial dysfunction is involved in many of the life-threatening complications of alloSCT, such as sinusoidal obstruction syndrome/venoocclusive disease, transplant-associated thrombotic microangiopathy, and refractory acute graft-versus host disease. This review delineates the role of the endothelium in severe complications after alloSCT and describes the current status of search for biomarkers predicting endothelial complications, including markers of endothelial vulnerability and markers of endothelial injury. Finally, implications of our current understanding of transplant-associated endothelial pathology for prevention and management of complications after alloSCT are discussed.

Bone Marrow Transplantation (2021) 56:2326–2335; <https://doi.org/10.1038/s41409-021-01390-y>

THE ENDOTHELIUM—A HINGE BETWEEN EXTRINSIC AND INTRINSIC NOXAE AND POST-TRANSPLANT COMPLICATIONS

The endothelium is a semipermeable monolayer of endothelial cells (EC) organized as a complex biological interface that separates all tissues from circulating blood. The vascular endothelium is a highly active organ involved in the regulation of the vascular tone, cellular adhesion and migration, coagulation, vessel wall permeability, and various inflammatory processes [1, 2]. In the setting of alloSCT, host ECs may also participate in adaptive immune responses [3].

During alloSCT, ECs are consecutively challenged by toxicities of the conditioning regimen and the drugs used for immunosuppressive prophylaxis, inflammatory molecules released by damaged cells and tissues, endotoxins due to damaged mucosal barriers, donor leukocyte engraftment, and alloreactive immune responses [3]. Individual responses of patients' ECs may be driven by both acquired endothelial distress (caused by comorbidities, pretreatment toxicity, etc.) and an intrinsic endothelial vulnerability (e.g. genetic polymorphisms [4]) (Fig. 1). Possible consequences are EC activation and injury that may progress to an irreversible state of endothelial dysfunction. In turn, a pro-inflammatory, pro-coagulant and pro-apoptotic process is triggered, manifesting as endothelial injury syndromes. Here we focus on the most prominent of them, namely sinusoidal obstruction syndrome/venoocclusive disease (SOS/VOD), transplant-associated thrombotic microangiopathy (TA-TMA), and refractory acute GVHD. Additional endothelial injury syndromes after alloSCT not addressed in this overview include i.a. vascular type idiopathic pneumonia syndrome [5], early fluid retention [6], early bilirubinaemia [7] posterior reversible encephalopathy syndrome, and several subtypes of chronic GVHD [8].

Biomarkers of selected endothelial injury syndromes after alloSCT

For delineating the pathogenesis, but also for diagnosis and prediction of the main endothelial injury syndromes VOD/SOS, TA-TMA, and refractory acute graft-versus host disease (GVHD), extensive efforts have been made to identify biomarkers of endothelial damage and dysfunction.

VOD/SOS

manifests as damage of sinusoidal ECs, resulting in the liver injury of various degrees. It is characterized by rapid weight gain, ascites, painful hepatomegaly, and jaundice [9, 10]. Several groups have focused on VOD/SOS-related endothelial biomarkers as summarized in Table 1 [11–16].

TA-TMA

is another endothelial syndrome associated with excess mortality in the early post-transplant period. TA-TMA may affect up to 25–30% allografted patients with up to 90% mortality rates in its most severe forms [17]. TA-TMA is characterized by the endothelial injury resulting in microangiopathic hemolytic anemia, platelet consumption, complement dysregulation, and thrombosis and fibrin deposition in the microcirculation [18].

Endothelial biomarkers for diagnosis or prognostication of TA-TMA are summarized in Table 1 [19–27]. Algorithms were proposed to identify high-risk patients most likely benefitting from targeted treatment interventions such as terminal complement blockade (Table 1). Inamoto et al. [28] introduced the concept of intestinal transplant-associated microangiopathy as a separate entity observed in patients with severe steroid-refractory diarrhea not meeting the clinical criteria of systemic TMA or GVHD.

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Received: 1 February 2021 Revised: 8 June 2021 Accepted: 22 June 2021

Published online: 12 July 2021

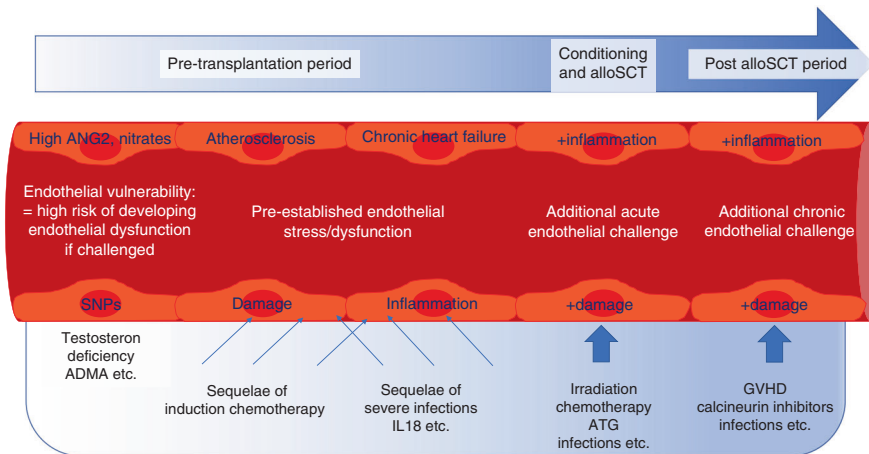


Fig. 1 Endothelial challenges during allogeneic stem cell transplantation. Endothelial cells experience stressing influences before, during, and after alloSCT. In the pre-transplantation period, patient-specific endothelial vulnerability and pre-established endothelial damage set the stage for the subsequent challenges during conditioning therapy, immune suppression, and post-transplant complications.

Acute GVHD

(aGVHD) is the most critical complication following alloSCT, in particular its steroid-refractory form, and represents one of the major causes of mortality. Its complex pathophysiology involves cytokine dysregulation and sequential activation of T cells and monocytes [29]. Upon damage by the early toxicities (conditioning, calcineurin inhibitors (CNI), donor leukocyte engraftment), the endothelium itself may also become a target for activated allogeneic T cells at the onset of aGVHD [3].

First histological evidence of immunologic vascular injury was retrieved from skin biopsies of patients suffering from cutaneous aGVHD, showing perivascular VWF deposition. In addition, loss of endothelial TM, increased expression of ICAM-1 and VCAM-1, and extravasation of vWF was observed in tissue specimens of patients with aGVHD, pointing to EC involvement (Table 1 [30–47]).

Another blood-derived endothelial biomarker considered for aGVHD is ANG2, both as a single marker [35, 48] and as part of a biomarker panel [46]. ANG2 was shown to be predictive for general endothelial damage-related transplant complications, and particularly for the development of treatment-refractory aGVHD (Table 1). Additional endothelial markers are summarized in Table 1.

Finally, ST2 has become an important focus of biomarker research for aGVHD prediction and prognostication [36, 40, 47, 49]. This marker also associates with TA-TMA [24, 27] and thus underlines the link between microangiopathy and lethal complications (Table 1).

FUNCTIONAL HETEROGENEITY OF SYSTEMIC ENDOTHELIAL CELL DYSFUNCTION—IMPLICATIONS FOR BIOMARKER STUDIES

Functional heterogeneity is a hallmark of the endothelial cell system [50, 51]. The hypothetical functional definition of ECs as input-output devices [50, 52] emphasizes their role as direct responders to a variety of challenges such as blood pressure, temperature, pH and oxygen pressure, and serum factors [51, 53]. Maintaining homeostasis of tissue perfusion is an important function of ECs that are continuously exposed to stimuli provided by the alternative complement pathway, coagulation factors, cytokines, activated platelets, leukocytes, and occasional infectious agents. Due to their distribution over space and time, hardly two ECs will be exposed to the same set of input signals [54]. Moreover, stochastic or inheritable

heterogeneous DNA methylation patterns add to the functional variability of seemingly “homogeneous” mature EC populations [55, 56]. Therefore, tissue-specific stress responses of ECs can explain that even during *systemic* EC dysfunction (e.g. due to CNI, viruses, irradiation etc.), microangiopathy develops *locally* in individual patients [54].

This functional heterogeneity has to be considered in all attempts to define clinical diagnostic criteria for endothelial complications after alloSCT. It also explains the difficulties in defining unequivocal diagnostic criteria for TA-TMA and VOD/SOS. E.g. for TA-TMA, based on expert opinion rather than biology, diverse consensus-defined cut-offs for creatinine, lactate dehydrogenase (LDH), platelet and schistocyte counts, weight gain, and bilirubin levels exist, resulting in discordant diagnostic systems with strongly diverging prognostic impact [20, 57–59].

Ideal markers should be capable of predicting endothelial dysfunction in different clinical settings. Not surprisingly, many endothelial biomarkers described in alloSCT, e.g. ST2 [60], ANG2 [61, 62], ADMA [63], Nitrates [64], TM [65], and others, also predict outcome in cardiovascular disorders. However, these markers were developed generally for diagnosis and/or prognostication of manifest clinical problems rather than for predicting systemic endothelial dysfunction as defined above. In contrast, the goal should be to find biomarkers indicating an increased endothelial risk even before the onset of endothelial complications, ideally before transplant. This risk could consist in a pre-existing subclinical or clinical endothelial defect conferring a generally increased likelihood of endothelial complications and mortality: *endothelial injury*. Alternatively, the risk could consist in the predisposition of an otherwise intact endothelium of becoming dysfunctional only after a triggering event such as GVHD or other second hits: *endothelial vulnerability* (Fig. 1).

Endothelial vulnerability and endothelial injury

In contrast to the immune system, which is usually completely replaced by cells of donor origin after alloSCT, ECs remain exclusively recipient-derived. This implies that pre-existing defects may impair post-transplant homeostasis of the endothelium and its capacity of enduring eventual challenges, such as the aforementioned noxae, but also the interaction between recipient ECs and donor immune cells and platelets.

The concept of *endothelial vulnerability* is based on the observation that serum markers of endothelial cell distress such

Table 1. Select studies on endothelial biomarkers in three endothelial complications after alloSCT.

Endothelial injury syndrome	Biomarker	Association direction	Specimen	Time point	Application	No. of patients	References
SOS/VOD	Soluble TM, P-selectin	Increased	Blood plasma	d0 to d + 52	Prediction	25	Catani et al. 1996 [12]
	Soluble TM	Increased	Blood plasma	day+15	Prediction	45	Testa et al. 1996 [16]
	Soluble TM, PAI-1	Increased	Blood plasma	d + 14	ns	28	Nurnberger et al. 1998 [14]
	VWF	Increased	Blood plasma	day0, day+7, day+14	Prognosis	24	Palomo et al. 2010 [15]
	VWF, soluble TM, soluble ICAM-1	Increased	Blood plasma and serum	day-1, day+7	Prediction ^b	38	Cutler et al. 2010 [13]
TA-TMA	5-marker panel: L-ficolin, HA, soluble ST2, ANG2, VCAM-1	Increased	Blood plasma	Onset of symptoms, d0	Diagnosis, prognosis (3-marker panel)	45, 35 ^c	Akil et al. 2015 [11]
	VWF	Increased	Blood plasma	After engraftment	ns	66	Holler et al. 1989 [19]
	VWF, t-PA	Increased	Blood plasma	d + 19	ns	25	Seeber et al. 1992 [25]
	VWF	Increased	Blood plasma	d + 50	ns	84	Kalhs et al. 1995 [22]
	VWF, soluble TM	Increased	Blood plasma	Onset of symptoms	Diagnosis	52	Zeigler et al. 1996 [26]
	VWF, soluble TM, t-PA	Increased	Blood plasma	d + 14	Prediction	16	Kanamori et al. 1998 [23]
	CFH autoantibodies	Increased	Blood plasma	After diagnosis	ns	3 a	Jodele et al. 2013 [21]
	Soluble terminal complement complex (C5b-9)	Increased	Blood serum	Onset of symptoms	Diagnosis, prognosis	90 ^d	Jodele et al. 2014 [20]
	Soluble ST2	Increased	Blood serum	Pre-transplant	Prediction	771	Zeisbrich et al. 2017 [27]
	Soluble ST2	Increased	Blood plasma and serum	d + 14	Prediction	95 ^{c,d} , 110 ^{c,d} , 107 ^{c,d}	Rotz et al. 2017 [24]
Acute GVHD	VWF	Increased	Skin biopsy ^e	Onset of aGVHD	Diagnosis	55	Dumler et al. 1989 [33]
	VWF	Increased	Skin biopsy ^e	Onset of aGVHD	ns	44	Sviland et al. 1991 [45]
	ICAM-1	Increased	Duodenal biopsy	Onset of aGVHD	ns	18	Roy et al. 1993 [42]
	VWF, VCAM-1	Increased	Skin biopsy ^e	Onset of aGVHD	Diagnosis	23	Shen et al. 1994 [44]
	VWF, soluble TM	Increased	Blood plasma	Onset of aGVHD	ns	50	Salat et al. 1997 [43]
	Soluble ICAM-1, E-selectin	Increased	Blood plasma and serum	d + 30	Prediction	49	Matsuda et al. 2001 [37]

Table 1 continued

ANG2, EMP	Increased	Blood plasma and serum	d + 28	Prognosis	26	Nomura et al. 2008 [41]
ANG2	Increased	Blood serum	Pre-transplant, onset of aGVHD	Prognosis	48	Luft et al. 2011 [35]
Endothelial TM	Decreased	Colon biopsy ^f	Onset of aGVHD	Diagnosis	51	Andrulis et al. 2012 [31]
ANG2	Increased	Blood serum	Pre-transplant	Prognosis	331	Dietrich et al. 2013 [32]
Bone marrow microvessel density	Increased	Bone marrow	Onset of aGVHD	ns	26	Medinger et al. 2013 [38]
Soluble ST2	Increased	Blood plasma	d + 14 and start of treatment	Prognosis	381, 296 ^c , 302 ^c , 75 ^c	Van der Lugt et al. 2013 [47]
Follistatin, PIGF	Increased	Blood plasma and serum	Onset of aGVHD, d + 28	Prognosis	34, 105 ^c , 158 ^c , 53 ^c	Holtan et al. 2015 [34]
4-marker panel: ANG2, soluble TM, D-dimer, CRP	Increased	Blood plasma	Onset of aGVHD	Prognosis	188	Tatekawa et al. 2016 [46]
VWF	Increased	Blood plasma	d + 7	Prediction	44	Mir et al. 2017 [39]
Soluble ST2, REG3 α	Increased	Blood plasma and serum	d + 14	Prognosis ^g	225	Nomura et al. 2017 [40]
CEC	Increased	Whole blood	Onset of aGVHD	Diagnosis	90	Almici et al. 2017 [30]
Soluble ST2, REG3 α	Increased	Blood plasma and serum	1 week after start of aGVHD treatment	Prognosis	236, 142 ^c , 129 ^c	Major-Monfried et al. 2018 [36]

aGVHD acute graft-versus-host disease, ANG2 angiopoietin 2, CEC circulating endothelial cells, CFH complement factor H, CRP C-reactive protein, HA hyaluronic acid, EMP endothelial cell-derived microparticles, ICAM-1 intercellular adhesion molecule 1, ns not specified, PAI-1 plasminogen activator inhibitor type-1, PIGF placental growth factor, SOS/MOD sinusoidal obstruction syndrome/venoocclusive disease, ST2 suppression of tumorigenicity 2, TA-TMA transplant-associated thrombotic microangiopathy, TM thrombomodulin, t-PA tissue-type plasminogen activator, VCAM-1 vascular cell adhesion molecule-1, VWF von Willebrand factor.

^aIn patients receiving sirolimus.

^bValidation cohort(s).

^cPediatric patients.

^dPatient age 0–30 years.

^ePerivascular extravasation of VWF.

^fLoss of endothelial TM expression.

^gPatients treated with recombinant soluble thrombomodulin.

as nitrates, ANG2, and ADMA, when elevated before conditioning therapy, are associated with increased NRM only in case of a second hit, namely aGVHD, but not in patients who do not develop aGVHD [32, 35]. Similarly, defined single nucleotide polymorphisms in *recipient* genes related to endothelial integrity, such as the TM and CD40Ligand genes, result in a significantly poorer outcome of patients with aGVHD, without affecting survival in the absence of GVHD [4, 66] (Table 2). This resembles other endothelial complications outside the transplant setting, such as atypical hemolytic-uremic syndromes (aHUS), that are based on pathogenic alterations in various components of the complement pathway but require additional challenges before actual endothelial cell dysfunction occurs [67]. This 2-step model of endothelial vulnerability is also supported by the observation that only a minority of patients with gastrointestinal GVHD shows loss of endothelial surface expression of TM as a sign of endothelial damage at disease onset, although serum CD141 levels subsequently increase in most refractory patients [31, 35]. This supports the view that pre-existing endothelial vulnerability paves the way for a

progressive microangiopathy developing under the stress posed by aGVHD, adding to organ damage and finally resulting in steroid refractoriness (Fig. 2) [35].

The lack of predictive power in patients without aGVHD is a strong hint that endothelial vulnerability markers do not reflect manifest endothelial damage. In contrast, endothelial markers measured pre-transplant or early post-transplant which are associated with an increased risk of NRM (or TMA as the common clinical end stage of endothelial damage) independent of GVHD can be considered as indicators of an *actually injured endothelium* associated with already manifest endothelial dysfunction. Examples for this type of markers are ST2 and IL18 [27, 68] (Fig. 1/ Fig. 2/ Table 2).

Because the triad of increased creatinine and LDH together with low platelet counts represents the cornerstone of TA-TMA diagnosis, we explored if the ratio of LDH*creatinine/platelets as a continuous, quantitative read-out, termed “Endothelial activation and Stress Index” or *EASIX*, could serve as easy-to-assess surrogate for measuring endothelial injury. Indeed, *EASIX* measured pre-transplant (*EASIX*-pre) predicts TA-TMA and NRM, *EASIX* measured on day 0 of transplantation (*EASIX*-d0) predicts SOS/VOD, and *EASIX* measured at the onset of acute GVHD (*EASIX*-aGVHD) predicts NRM [69–72]. In addition, *EASIX*-pre and *EASIX*-d0 correlate with newly recognized syndromes of endothelial cell dysfunction such as early fluid retention [6] and early hyperbilirubinaemia (irrespective of SOS/VOD) [7].

Similar to established endothelial dysfunction markers, *EASIX*-pre predicts outcome also in patients without aGVHD [71, 72]. Accordingly, *EASIX*-pre correlates with markers of endothelial injuries, such as IL18, and low IGF1, but not with vulnerability markers [71] (Table 2). In conclusion, *EASIX* is a readily available indicator of actual endothelial dysfunction throughout the whole peritransplant period. Its applicability in non-transplant clinical settings, such as prognostication of lower risk myelodysplastic syndromes [73], multiple myeloma [74], CAR-T cell therapy, chronic heart disease, and COVID-19 is currently being explored.

Table 2. Characteristics of endothelial vulnerability and endothelial injury.

Endothelial vulnerability	Endothelial injury
No impact on outcome without aGVHD	Predicts NRM with and without aGVHD
SEP normalizes risk of NRM	No impact of SEP on NRM
ANG2, nitrates, ADMA, SNPs in THBD and CD40L	<i>EASIX</i> , IL18, testosterone deficiency (men)

aGVHD acute graft-versus-host disease, *SEP* statin-based endothelial protection, *NRM* non-relapse mortality, *ANG2* angiotensin-2, *ADMA* asymmetric dimethyl arginine, *SNPs* single nucleotide polymorphisms, *THBD* thrombomodulin, *EASIX* endothelial activation and stress index, *IL18* interleukin-18.

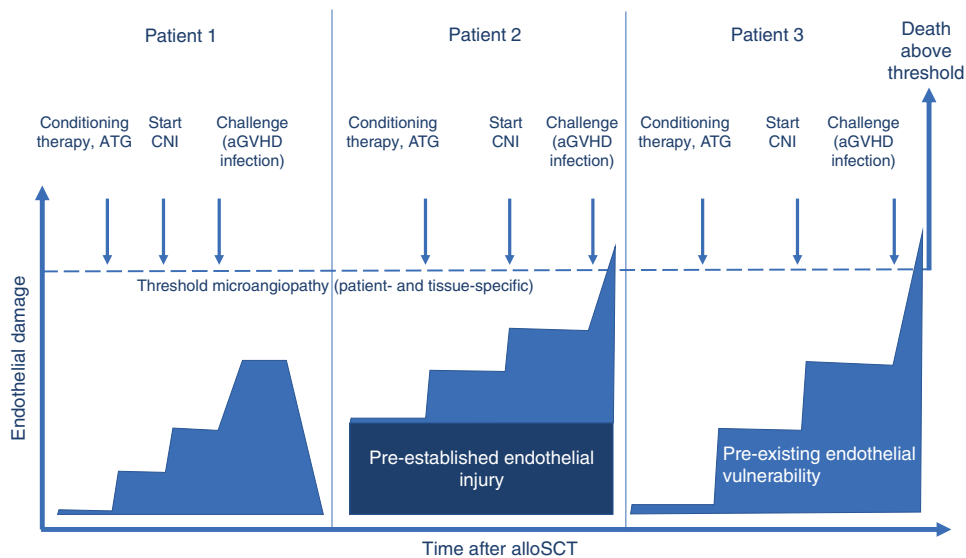


Fig. 2 Hypothetical link between pre-established endothelial cell injury and endothelial vulnerability with mortality after alloSCT. Conditioning therapy, immunosuppressive drugs, and post-transplant complications increase endothelial cell distress. In most patients, the threshold to substantial endothelial dysfunction, disturbed microcirculation/microangiopathy and death will not be trespassed (patient 1). Patient 2 with pre-established endothelial cell injury responds similarly to the additional endothelial strains in the context of alloSCT. However, the threshold will be reached due to a lower area of resilience. Patient 3 without pre-established endothelial injury responds more vigorously to the same endothelial challenges due to a patient-specific endothelial vulnerability. The net effect is again an infringement of the threshold and severe complications/death.

Management implications

Regarding therapeutic interventions for endothelial damage, defibrotide is currently the only approved drug for the treatment of hepatic SOS/VOD. In a historically controlled multicenter open-label phase-III study [75] a significantly better day +100 survival following alloSCT was observed in the defibrotide arm (38%) compared to controls (25%). Results from a compassionate-use [76] and expanded-access treatment program [77] could further verify the efficacy and safety of defibrotide for the treatment of post-transplant SOS/VOD. For a more detailed review on defibrotide treatment and other recent advances in the therapy of endothelial syndromes see references 78–80.

Obviously, the hen-and-egg dilemma—namely whether endothelial defects are cause or consequence of transplant-related complications—is still not completely solved. However, the evidence outlined in the previous section suggests that a pre-existing endothelial aberration is often present, either latent as vulnerability, or as manifest injury (Fig. 1). If this conclusion is correct, in addition to therapeutic strategies, prophylactic or pre-emptive measures for endothelium protection at least in those patients who have a biomarker profile suspicious of endothelial vulnerability are highly warranted.

EC-protective drugs that have been explored include statins, ursodeoxycholic acid (UDA), and defibrotide [4, 27, 69, 81–89]. Regarding statins, preliminary evidence suggests that statin prophylaxis with or without UDA is safe and can reduce the risk of TA-TMA, SOS/VOD, and refractory aGVHD, thereby decreasing NRM (Table 3). Prophylactic UDA reduced NRM and severe aGVHD in a prospective randomized study [89]. Defibrotide prophylaxis reduced the risk of SOS/VOD and aGVHD in a large pediatric prospective randomized trial with a favorable safety profile [86, 90]. Although conclusive rating of the evidence provided by these studies is hampered by considerable heterogeneity of study design, endpoints, and often small sample size, the bottom-line is that there appear to be some efficacy signals for endothelium protection by all three drugs.

To this end, in 2010 we introduced a statin-based endothelial protection (SEP) combining UDA and pravastatin as institutional routine policy for all patients admitted for alloSCT. This was associated with attenuation of excess NRM in aGVHD patients with biomarkers of endothelial vulnerability, whereas NRM in patients without evidence for endothelial vulnerability remained unchanged (Table 3). Notably, incidences of SOS/VOD and TA-TMA were also reduced in patients with SEP, as compared to (non-randomized) controls [27, 69, 71].

Thus, although randomized studies are missing, the combination of statins and UDA appears to have the capacity to alleviate the complications linked to endothelial vulnerability, but not to repair manifest severe endothelial injury (Table 2). Therefore, new approaches are necessary for the prevention and treatment of endothelial dysfunction caused by pre-existing endothelial damage. Two obvious principle strategies (which are not mutually exclusive) for achieving this will be detailed in the following: a) re-shaping anti-neoplastic and immunosuppressive regimens in order to preserve endothelial integrity; and b) exploring novel agents for endothelial protection or repair for patients with established endothelial dysfunction.

ADJUSTING ANTI-NEOPLASTIC AND IMMUNOSUPPRESSIVE REGIMENS TO ENDOTHELIAL CELL FUNCTION

Here, two basic questions have to be addressed: first, where does the pre-existing endothelial lesion derive from - and second, to which extent do conditioning regimens, blood pressure medications, antibiotic, antiviral and antifungal drugs, and

immunosuppression add to impairment of physical and functional endothelial integrity in individual patients?

The first question requires a thorough work-up of the endothelial toxicity of agents commonly used in the pre-SCT setting, such as fludarabine, alkylators, and anthracyclines, but also irradiation [91, 92], but of course also of the contributions of vascular comorbidity unrelated to the neoplastic disease. Regarding the second question, a large variety of drugs frequently employed during or after SCT, such as CNI, sirolimus, calcium channel blockers, and angiotensin-II inhibitors can affect endothelial integrity and may demand patient-based endothelial monitoring [93–96]. Because of its easy accessibility, also for retrospective analyses, EASIX might be a particularly useful tool for this purpose.

HOW TO EXPLORE NOVEL ENDOTHELIAL PROTECTIVE AGENTS

There is a paucity of agents with the capacity of protecting or restoring EC integrity. Given the potential side effects of novel drugs being explored for this purpose, high-risk populations who are most in need of such medications need to be identified. Our experiences with SEP show that endothelial protection may differ for endothelial vulnerability settings and manifest endothelial cell injury. Similarly, the reported benefits of defibrotide and—in children—C5 inhibitors (e.g. Eculizumab [97]) will have to be analyzed for differential efficacy in patients with different endothelial risk. In adult patients, serious toxicities, e.g. fatal infections with complement C5 inhibitors [98, 99], strongly discourage using this approach outside of clinical trials.

In addition to searching for novel EC-promoting agents, we should also consider incorporating the established knowledge of cardiovascular medicine for endothelial protection, e.g. by investigating pre-emptive use of statins, beta-adrenergic antagonists, angiotensin-converting enzyme inhibitors, acetyl salicylate, or N-acetylcystein [100] amongst others, in patients with evidence for endothelial injury. The EASIX toolkit seems to be particularly practical for classifying endothelial risk for this purpose.

CONCLUSION

EC dysfunction syndromes are increasingly recognized as important contributors to mortality and morbidity after alloSCT. Although their pathogenesis is not uniform and the overwhelming functional heterogeneity of EC can channel systemic endothelial disorders into tissue-specific, local micro-angiopathies, the common final path of EC dysfunction syndromes is a severe and mostly irreversible alteration of EC integrity. There is growing evidence that the manifestation of clinically effective EC disintegration is at least partially driven by distinct pre-existing endothelial defects which can be defined as endothelial vulnerability and endothelial injury, respectively. Whereas endothelial injury represents manifest lesions resulting in permanent endothelial dysfunction, endothelial vulnerability describes latent defects translating into endothelial dysfunction only upon a second hit. These two conditions can be distinguished by biomarker profiling with a prominent role for EASIX. While endothelial vulnerability might potentially be overcome by prophylactic use of endothelium-protective drugs, such as statins and UDA, effective tools for treating manifest endothelial damage—except for defibrotide in specific settings—are missing. Thus, novel approaches to target endothelial injury and its devastating clinical sequelae appear to be a high-priority goal in order to reduce the risks of allo-SCT.

Table 3. Select studies on intended or incidental prophylaxis with endothelium-protective drugs in allo-SCT.

Drug	Study type and objective (application)	Number of patients	Target population	Outcomes	References
Miscellaneous statins	Retrospective; post-transplant hyperlipidaemia (incidental)	No statins: 541, statins: 220	recipients RD, UD	Grade II-IV aGVHD significantly increased in patients with hyperlipidaemia; statins reduced hyperlipidaemia without significant side effects	Blaser et al. 2012 [81]
Miscellaneous statins	Retrospective; incidence and severity of aGVHD (incidental)	No statins: 57, statins: 10	Recipients (AML, ALL)	Trend to less aGVHD (II-IV) in the statin group ($p = 0.08$), no effect on cGVHD, no effect on GVL	Hamadani et al. 2008 [83]
Atorvastatin	Prospective single arm; safety; grade II-IV aGVHD (intended)	Statins: 69; 30 (MRD) 39 (MUD)	Recipients	No negative safety signals; preliminary positive efficacy signals.	Kanate et al. 2017 [85]
Miscellaneous statins	Retrospective; GVHD risk (incidental)	No statins: 464, statins: 75	Donors and/or recipients, RD	Grade III-IV aGVHD significantly reduced with donor statin treatment; trend for less NRM with recipient statin treatment; effects seen only with CSA	Rotta et al. 2010 [87]
Miscellaneous statins	Retrospective; GVHD risk, NRM, Relapse, mortality (incidental)	No statins: 1130; statins: 76	Recipients, RD and UD	Chronic GVHD significantly reduced but relapse risk increased with statins; effects seen only with CSA; no statin effect on any other endpoint	Rotta et al. 2010 [88]
Atorvastatin	Prospective single arm; safety; grade II-IV aGVHD (prophylactic use)	Statins: 30	Donors and recipients, RD	No negative safety signals; preliminary positive efficacy signals.	Hamadani et al. 2013 [84]
UDA	Prospective randomized; chronic GVHD and survival outcomes (intended)	No UDA: 119 UDA: 123	Recipients, RD and UD	Grade III-IV aGVHD significantly reduced and NRM and OS significantly improved with UDA; no significant effects on chronic GVHD and relapse risk	Ruutu et al. 2014 [89]
Pravastatin ± UDA	Retrospective cohort comparison; TA-TMA, refractory aGVHD (intended)	No statins/UDA: 356 statins/UDA: 415	Recipients, RD and UD	TA-TMA, refractory aGVHD significantly reduced with statins/UDA	Zeisbrich et al. 2017 [27]
Pravastatin ± UDA	Retrospective cohort comparison; SOS/VOD (intended)	No statins/UDA: 826, statins/UDA: 359	Recipients, RD and UD	SOS/VOD significantly reduced with statins/UDA; effect most pronounced in the highest EASIX quartile	Jiang et al. 2020 [69]
Pravastatin ± UDA	Retrospective cohort comparison; survival outcomes (intended)	No statins/UDA: 576 statins/UDA: 344	Recipients, RD and UD	NRM reduced with statins/UDA	Rachakonda et al. 2018 [4]
Defibrotide ± UDA	Prospective randomized; SOS/VOD (intended)	Defibrotide: 180, No defibrotide: 176	Recipients, autologous and allogeneic, pediatric only, high risk	SOS/VOD reduced with defibrotide; grade I-IV aGVHD significantly reduced with defibrotide; no negative safety signals including bleeding events; no effect on TA-TMA, NRM, and overall mortality	Corbacioglu et al. 2012 [82]
Defibrotide + UDA	Retrospective; SOS/VOD (intended)	Defibrotide: 63	Recipients (adult, high risk)	No negative safety signals except for bleeding events in 22%; preliminary positive efficacy signals	Picod et al. 2018 [86]

aGVHD acute graft-versus-host disease, cGVHD chronic graft-versus-host disease, GVL graft-versus-leukemia, NRM non-relapse mortality, RD related donor, SOS/VOD sinusoidal obstruction syndrome/venoocclusive disease, TA-TMA, transplant-associated thrombotic microangiopathy, UD unrelated donor, UDA ursodeoxycholic acid.

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FUNDING

Open Access funding enabled and organized by Projekt DEAL.

COMPETING INTERESTS

T.L. and A.R. have nothing to disclose. P.D.: consultancy for AbbVie, AstraZeneca, bluebird bio, Gilead, Janssen, Novartis, Riemser, Roche; speakers bureau for AbbVie, AstraZeneca, Gilead, Novartis, Riemser, Roche; research support from Riemser.

ADDITIONAL INFORMATION

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