Endothelial Dysfunction after Hematopoietic Stem Cell Transplantation

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Endothelial dysfunction (ED) is frequently encountered in transplant medicine. After hematopoietic stem cell transplantation (HSCT), ED participates in the pathogenesis of various complications such as sinusoidal obstruction syndrome/veno-occlusive disease (SOS/VOD), graft-versus-host disease (GVHD), transplant-associated thrombotic microangiopathy (TA-TMA), idiopathic pneumonia syndrome (IPS), capillary leak syndrome (CLS), and engraftment syndrome (ES).

endothelial dysfunction | hematopoietic stem cell transplantation (HSCT) | Therapeutic Interventions | Clinical

1. Introduction

The endothelium is a thin structure composed of a monolayer of flattened cells, covering the inner part of blood vessels and playing a pivotal role in vascular homeostasis [1]. The endothelium is provided with molecules and mechanisms with antithrombotic and anti-inflammatory functions and a set of molecules that retain prothrombotic properties. A balance among them maintains normal antithrombotic and anti-inflammatory status [2].

The shift from the basal state to the procoagulant and inflammatory condition is referred to as endothelial activation; prolonged endothelium activation will lead to endothelium dysfunction (ED).

ED refers to the inability of endothelium cells (ECs) to determine vasodilatation of the vessel wall. ED is associated with reduced nitric oxide (NO) production, increased adhesiveness of leukocytes and platelets, increased endothelium permeability, and finally, apoptosis of EC [3]. ED is believed to play an essential role in cardiovascular diseases, renal diseases, infections, liver diseases, and multiorgan failure [4]. More widely, dysfunction of the vascular endothelium has been considered a hallmark of human diseases [1]. Notably, an endothelial activation induced by cytokines may contribute to the pathophysiology of COVID 19 disease [5][6][7].

ED is also frequently found in many complications arising in transplant medicine [8]. After allogeneic hematopoietic stem cell transplantation (HSCT), many clinical factors play pathogenetic roles in ED. Some are common to other clinical settings such as advanced age, diabetes, hypertension [9][10]. However, others such as alloreactivity, infections, immunosuppressive agents, and, in HSCT, pretransplant conditioning are specific to the transplanted patients [11][12].

The term alloreactivity is widely accepted and used. Immunological reactions after an allogeneic HSCT are heterogeneous and may determine ED by different mechanisms. Class I and II histocompatibility antigens, expressed on EC, may be the targets of immunologic attack [13]. The expression of class II antigens in EC is induced by γ interferon and down modulated by fluvastatin and everolimus [14].

After solid organ transplantation, antibody-mediated rejection is believed to represent antibody and complement-dependent injury to the microvasculature. When rejection is diagnosed after solid organ transplantation, the alloimmune reaction is readily apparent from the histopathology of the transplanted organ (leukocytes infiltrate, vascular damage, complement deposition, thrombosis) [15][16]. It results in allograft dysfunction, allograft loss, and accelerated graft vasculopathy [17]. However, in the rejection setting, the immunological mechanisms may also involve a cytotoxic T-cell response or NK response [16][18].

After allogeneic HSCT, the target of an alloimmune attack can be, at least theoretically, the entire vascular tree of the recipient. For instance, and as proof, graft-versus-host disease (GVHD) is associated with endothelium damage characterized, at the immunohistochemistry level, by perivascular infiltrate of activated lymphocyte and by an increased level of von Willebrand factor (v-WF) [19]. However, at gross histopathology, the evidence of alloimmune reaction is scarce. The reasons for that paucity have not yet been clarified [20].

Although alloimmunity can be the initiating trigger, other mechanisms besides direct cytotoxicity may occur, and innate immunity may take part in tissue damage without any histologically visible cellular effector mechanism [21]. In the context of innate immunity, the release of cytokine, along with the activation of complement and Toll-like receptors, is a potent mediator of tissue damage. In determining ED, infections or administration of pharmacologic agents may also act as important cofactors.

A three steps model has been proposed [22]. Predisposition for ED may be the first step. Conditioning and tissue damage (second steps) act on this baseline status to determine subclinical ED. Finally, as the third step, alloimmunity or infections or pharmacological agents may further increase the prothrombotic/proinflammatory status, causing the full-blown clinical picture.

2. Clinical Pictures of Endothelial Dysfunction after Allogeneic HSCT

From the clinician’s point of view, the involvement of endothelium after allogeneic HSCT is frequent and may manifest in practice, with different clinical pictures. This issue has been the object of several reviews during the last decade [12][23][24]. A number of organ-specific diseases such as SOS/VOD, IPS, CLS, ES, and TA-TMA have their pathogenesis in EC dysfunction. All these diseases may terminate in multiorgan failures (MOFs). However, there is no agreement on which clinical picture has to be considered as derived from systemic endothelial dysfunction [24]. Primarily, venous-occlusive disease, capillary leak syndrome, and engraftment syndrome are not considered by all researchers as dependent on a systemic endothelial dysfunction [24]. In contrast, some researchers retain that EC has a relevant role in corticosteroid-refractory acute graft-versus-host disease.

2.1. SOS/VOD

SOS/VOD is characterized by increased bilirubin, body weight increase due to liquid retention, and painful liver enlargement. Conditioning intensity and conditioning type play significant roles, together with age, underlying diagnosis, and the state of liver parenchyma [25]. The main histopathological findings are round-up of EC, EC detachment, and downstream embolization of EC, together with hemorrhage in Disse space and narrowing of the centrum-lobular vein [26]. The increase in body weight, which can reach 10–20% of the basal value, and the lack of response to diuretic treatment, demonstrate that, in this disease, endothelium damage is systemic. Severe forms of SOS/VOD may progress to multiorgan failure with renal, lung, or CNS toxicity, thus confirming the systemic nature of this disease. SOS/VOD is more frequent in conditions of increased HLA distance between donor and recipient, but no concomitant and overt a-GVHD is evident in most of these cases.

In SOS/VOD, nitric oxide synthase activity is reduced in liver cells [27]. HMGB-1 has been found to be involved in models of VOD induced experimentally by monocrotaline [28]. An upsurge in the level of HMGB-1 follows the administration of Monocrotaline. Activation of endothelium cells in VOD is demonstrated by an increased level of vWF, ICAM1, VLA4, and Ang-2 [29].

2.2. Capillary Leak Syndrome (CLS)

An increase in body weight, blood pressure reduction, tachycardia, and sudden decrease in serum albumin is the cluster of clinical abnormalities found in capillary leak syndrome. In the idiopathic form, a monoclonal immunoglobulin is frequently present in the plasma. Secondary CLS may be associated with severe infections or with the administration of pharmacological agents, such as interleukin-2, GM-CSF, gemcitabine, and monoclonal antibodies anti-CD19 and anti-CD22. High serum levels of Ang-2 and VCAM1 have been found in patients affected by idiopathic CLS.

A significant increase in body weight (>2.5%) has been reported after allogeneic HSCT in 20–30% of all patients [30]. Severe hydric retention is associated with reduced survival and a higher risk of severe GVHD [31]. Patients at risk for CLS at the start of conditioning may be identified as having a high EASIX score [32].

2.3. Idiopathic Pneumonia Syndrome (IPS)

IPS criteria include evidence of widespread alveolar injury with symptoms and signs of pneumonia in the absence of active lower respiratory tract infection. Diagnosis is made after the exclusion of commonly found pulmonary infections. It requires an intensive diagnostic workup, including at least a bronchoalveolar lavage. Alloreactivity toward lung tissue after HSCT in SCID mice is accompanied by signs of activation of lung EC [33]. Further, in the development of experimental IPS, an injury to the vascular endothelium has been observed [34]. Vessels in the lung are surrounded by a dense mononuclear cell infiltrate. There is apoptosis of ECs, presence of activated cytoplasmic caspase 3, and TUNEL positivity of nuclei. Cytotoxicity via the Fas-FasL pathway contributes to the development of experimental IPS. A role for TNF alpha has been hypothesized [35]. The expression of ICAM-1, VCAM-1, and eNOS are increased in lung biopsies of patients developing IPS [36].

However, over half of the patients diagnosed with IPS have a virus detected in bronchoalveolar lavage (BAL) samples [37]. The significance of these viruses in the pathogenicity of pneumonia remains unclear, although emerging evidence suggests that at least in the case of human herpesvirus 6 (HHV-6), these viruses may lead to lung injury and raises plausible concern that IPS may have been misdiagnosed in earlier studies. Alloimmune reactions toward lung tissue and infections may interact and be cofactors.

An imbalance between Ang-1 Ang-2 may also have a role in IPS. This imbalance has been found in ARDS [38]. A four-endothelial biomarker panel, including elevated angiopoietin-2/angiopoietin-1 ratio, vascular cell-adhesion molecule, and von Willebrand factor, is useful in identifying acute respiratory distress syndrome [39].

2.4. Engraftment Syndrome (ES)

Diagnostic criteria for engraftment syndrome, according to T. Spitzer, include major criteria (non-infectious fever, skin rash, and non-cardiogenic pulmonary edema) and minor criteria (weight gain, hepatic/renal dysfunction, or transient encephalopathy) [40]. Diagnosis is reached with the development of two or more of the previously cited symptoms within 96 h of the start of neutrophil recovery (absolute neutrophil count > 100). According to Maiolino, diarrhea is a further criterion of this syndrome. In the time frame of peri-engraftment, it is possible also to observe lung abnormalities such as diffuse ground-glass opacities, often with septal thickening and small pleural effusions [41]. ES has been described after autologous transplantation in patients mainly affected by multiple myeloma, POEMS syndrome, amyloidosis, and autoimmune diseases [42][43]. ES is, however, possible in patients affected by other underlying diagnoses.

The distinction between ES and autologous GVHD is difficult since both syndromes may present the involvement of the skin and diarrhea. Indeed, the relationship between autologous GVHD and ES is still debated, and these two clinical pictures may represent the same disease. ES has overlapping signs also with capillary leak syndrome.

ES is frequent after syngeneic HSCT [44]. ES has also been described after allogeneic HSCT. Indeed, not-infectious fever and manifestations of a vascular leak (edema with weight gain) may occur during granulocyte recovery in both the auto- and allotransplantation settings [45]. ES may precede a-GVHD, these two diseases being temporally associated, or ES may represent an initial stage of a-GVHD [46]. Therefore, in the allogeneic setting, the distinction of ES and a-GVHD is a matter of debate.

2.5. Transplant-Associated Thrombotic Microangiopathy (TA-TMA)

Micro-angiopathic anemia is a predominating feature. Clinical and laboratory signs are anemia, schistocytes, hemolysis, increase in LDH and decreased haptoglobin, hypertension, fever, decreased renal function, and proteinuria [47][48][49]. It may involve the kidney, the central nervous system, and the intestinal tract, and can be associated with pulmonary hypertension and serosal surface effusions.

According to Jodelle, it may present in a severe form in up to 18% of all patients in a pediatric population. TRM in patients having signs of the disease may be as high as 48%.

TA-TMA has been considered an endothelial form of a-GVHD. In most of these cases, a previous a-GVHD episode is present, or a-GVHD at the time of TA-TMA diagnosis is still ongoing, although with apparently minimal clinical signs [50]. However, TA-TMA may also appear after autologous HSCT. The pretransplantation patient's risk factors are a-GVHD, previous transplantation, MUD donor, and myeloablative conditioning [51][52].

In some cases, calcineurin inhibitors are significant contributors, and regression of signs has been reported after their discontinuation [48], although this remains a controversial issue [52]. In some other cases, infections may play essential roles as cofactors (aspergillus, HHV6, BK, adenovirus, CMV).

Intestinal TA-TMA is characterized by abdominal pain and may cause significant gastrointestinal bleeding. Differential diagnosis from intestinal a-GVHD may be problematic. Nishida et al. showed that intestinal thrombotic microangiopathy might mimic clinically a progressive a-GVHD [53]. Histopathology of intestinal biopsy shows microangiopathic changes in the gastrointestinal vasculature. Histologic features include endothelial cell swelling, endothelial cell separation, perivascular mucosal hemorrhage, intraluminal schistocytes, intraluminal fibrin, intraluminal microthrombi, loss of glands, and total denudation of mucosa [54][55].

Laskin et al. have reported complement activation after TA-TMA in HSC transplantation. These researchers found in renal biopsy C4d in the vessel [56]. Indeed, complement activation has been demonstrated in this type of TMA with an increase in C5b-9 [57][58]. Subsequently, similar complement regulatory defects to those found in a-HUS were identified in a small series of pediatric patients affected by TA-TMA [59].

Complement activation due to genetic deletion of CFI and CFH has also been demonstrated in children suffering transplant-associated thrombotic microangiopathy [60]. However, further confirmations of this physiopathological view are needed, in children as well as in adults.

A two-step pathogenetic process of TA-TMA may be hypothesized. Genetic abnormalities such as deficiency of complement regulatory proteins (CFI, CFH, complement genes CFHR1-CFHR3) may be predisposing factors. Subsequently, high dose chemotherapy, a-GVHD, factor H autoantibody, or infections will lead to endothelium damage and complement activation [61][52][59][62].

A reduced level of NO has also been found in TA-TMA [63]. High levels of NET predict TA-TMA; NETosi can determine complement activation and deposition of C5b-9. In TA-TMA, the immunosuppressive agents and infections are suspected of contributing as copathogens [64][65].

The concentration of soluble products derived from complement activation (C5b-9, C3a) may be measured in plasma. It could help in predicting the diagnosis and severity of TA-TMA [57][66][67][68].

2.6. Endothelial Dysfunction and GVHD

Conditioning and a-GVHD are linked to cytokine secretion and endothelium dysfunction. vWF levels measured after conditioning anticipate and predict GVHD [69]. A high level of Ang-2 at the start of conditioning and later early

after transplantation also predicts GVHD and TRM. Ang-2 levels since admission are higher in patients who will develop a-GVHD. Ang-2 remains high in patients affected by corticosteroid-refractory GVHD, while it is reduced in patients responding to treatment of GVHD. Endothelium damage is an important mechanism in the physiopathology of the disease, and it is FAS driven. There are some situations in which ED manifest during severe and protracted a-GVHD.

Patients with corticosteroid-refractory a-GVHD exhibited elevated serum levels of Ang-2, sTM, HGF, and IL-8 post-transplantation, compared with patients with sensitive a-GVHD and patients without a-GVHD (Dietrich et al. 2013). A high level of Ang-2 persisting after first-line therapy is a marker of corticosteroid-refractory GVHD [70], and ED may explain gastrointestinal signs and symptoms in these patients. Luft hypothesized that endothelial cell vulnerability and dysfunction, rather than refractory T-cell activity, drive the pathophysiology of corticosteroid-refractory GVHD [22][70].

A double hit has been proposed. In patients having a high Ang-2 level at pretransplantation (first hit), the occurrence of severe GVHD (second hit) will be followed by a risk of high NRM and a poor prognosis [71]. These data underline that endothelium damage may have an essential role in GVHD pathophysiology, especially in corticosteroid-refractory patients.

3. Therapeutic Interventions for EC Dysfunction

3.1. Defibrotide

Defibrotide is indicated in the severe form of SOS/VOD. In the INT study, the complete remission rate that can be achieved will depend on the age and the presence of MOF, and it varies between 40% and 70% [72]. Very severe forms of SOS/VOD have an unsatisfactory outcome [73].

In vitro activity on endothelial cells has been extensively studied, and it can reduce endothelial activation by lowering adhesion molecules expression and leukocyte adherence in several experimental models [74].

Defibrotide use has been explored in TM-TMA; in a limited number of patients affected with TM-TMA, the administration of a low dosage of defibrotide induced disease remission in all cases [75]. In a small study (ClinicalTrials.gov NCT03384693), administration of defibrotide as prophylaxis of TA-TMA resulted in very low NRM. The use of defibrotide as prophylaxis for acute GVHD in patients showing high risk has been proposed since a pediatric study found a reduction in transplantation toxicity and a reduction in severe GVHD [76]. In an experimental mouse model, prophylaxis with defibrotide reduces acute-GVHD and improves survival [77].

3.2. Anti-complement Agents

Blocking the complement system with eculizumab is currently the most effective treatment to circumvent the poor outcome in patients with severe TA-TMA [78].

In 2014, Jodelle reported that six patients were treated using eculizumab and 4/6 responded [79]. A single-center study reported eculizumab effective in 50% of adult patients, and a-GVHD was the only factor associated with inferior results [80].

At MD Anderson, in 5 years, 10 patients received eculizumab in an uncontrolled and retrospective study [81]. The anti-complement agent was associated with a change in immunosuppression. The OS in the eculizumab-treated cohort was better, compared with patients not receiving eculizumab. After transplantation, patients require modification of the dose according to CH50.

A recent meta-analysis on 116 patients suggests that eculizumab improves overall survival and response rate in patients with TA-TMA [82]. However, randomized, controlled trials and prospective studies are needed.

Narsoplimab is a monoclonal antibody able to inhibit MASP-2. It has been found effective in thrombotic microangiopathy of COVID-19 patients [83]. Narsoplimab has been studied in the treatment of IgA nephropathy, a disease in which the lectin pathway of complement is involved; narsoplimab reduced the progression of this kidney disease [84][85]. Narsoplimab has also been studied in TA-TMA, and preliminary results have been reported (EHA 2018).

Since these anti-complement agents have high costs, there is a need for diagnostic tests that can guide after allogeneic HSCT the selection of patients to be treated.

3.3. Anti-CD20 (Rituximab)

This agent is currently employed in cases of TMA not responsive to plasma exchange [86].

Moreover, it is used in the setting of TMA associated with LES [87]. Some cases of patients affected by TA-TMA and improvement after treatment with anti-CD20 have been reported [88][89][90]. In recipients after transplantation, the development of antibodies against factor H [59] might be an indication of anti-CD20 treatment.

3.4. Withdrawal of Calcineurin Inhibitors

Cyclosporin (CSA) modifies the endothelium, and it increases the synthesis of thromboxane A2 while decreasing the production of prostacyclin (PGI-2) [91][92].

CSA inhibits NOS [93]. Disturbances in constitutive and inducible NOS in the vascular wall may predispose to vasospasm, contributing to hypertension and vascular diseases. CSA inhibits angiogenesis induced by vascular endothelial growth factor (VEGF); VEGF activates the transcription of COX2, and CSA [69] inhibits this effect of VEGF on cyclooxygenase (Cox)-2 [94]. On this basis, withdrawal of CSA or switching to tacrolimus has been advocated in patients affected by TA-TMA [95]. However, other data do not support the usefulness of this practice [52].

3.5. Therapeutic Plasma Exchange

Therapeutic plasma exchange (TPE) has been widely used in treating TA-TMA since the procedure is active in TTP disease (Moschowitz's disease). However, its efficacy in the TA-TMA setting is limited, with response varying in the literature from 25% to 75% [96][97][98]. Clinically, the improvement is observed on the serum level of LDH and transfusion requirement, but survival remains very poor [98]. In TA-TMA patients, TPE is not able to prevent evolution into chronic kidney disease [99]. Moreover, the rate of complication of TPE is significant [100][101][102].

3.6. Thrombomodulin

TM has been found clinically helpful as a therapy for DIC in children [103][104][105] and for ARDS [106]. After allogeneic hematopoietic stem cell transplantation, a study reported that TM administration significantly reduced a-GVHD and ameliorated OS [107]. This result has been confirmed in a subsequent study [108]. TM has been found effective, after allogeneic HSCT, in cases of TA-TMA, SOS/VOD, and ES [109][110][111][112][113][114][115].

3.7. Statins

They are active in various diseases based on endothelial dysfunctions, such as cardiovascular disease and rheumatoid arthritis [116]. Statins have pleiotropic effects and can increase NO production in EC [117][118]. In a mice model, statins ameliorate the histopathologic signs of GVHD injury [83]. Statins increase the levels of Ang-1 [119]. In humans, prophylaxis using pravastatin after allogeneic HSCT reduces the incidence of SOS/VOD [120].

3.8. Angiopoietin1 Mimetics

Vasculotides is an Ang-1 mimetic provided with an anti-inflammatory effect. In animal models, it has been found to be helpful in various conditions such as hemorrhagic shock, pneumonia [121][122], strokes [123][124], and in preventing pathologic vascular leakage [125][126].

3.9. Alpha-1Anti-Trypsin (A1AT)

A1AT has an inhibitory effect on the expression of genes induced by TNF-alpha in endothelial cells, thereby reducing endothelial cell activation [127]. A1AT is also able to reduce the harmful effects of heme on EC [128]. Additionally, A1AT has immunoregulatory effects and decreases the production of IL-8, IL-6, TNF-a, and IL-1b. It promotes the differentiation and expansion of FoxP3+ regulatory T cells (Tregs).

A1AT has a demonstrated role in treating corticosteroid-refractory acute GVHD. Their anti-inflammatory and immunoregulatory effects merit further studies in treating complications based on ED in the transplantation setting [129].

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