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Advances in diagnosis and treatment of disseminated intravascular coagulation

Advances in the diagnosis and treatment of disseminated intravascular coagulation in haematological malignancies

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Abstract
Haematological malignancies, including acute leukaemia and non-Hodgkin lymphoma, are one of the underlying diseases that frequently cause disseminated intravascular coagulation (DIC), an acquired thrombotic disorder. Concomitant DIC is associated with the severity of the underlying disease and poor prognosis. The Japanese Society on Thrombosis and Hemostasis released the new DIC diagnostic criteria in 2017. This criteria include coagulation markers such as soluble fibrin and the thrombin-antithrombin complex to more accurately evaluate the hypercoagulable state in patients. Among several groups of anticoagulants available, recombinant human soluble thrombomodulin is most frequently used to treat DIC caused by haematological malignancies in Japan. DIC is remitted in parallel with the improvement of the underlying haematological diseases; thus, there is room for debate regarding whether the treatment of DIC would improve the prognosis of patients. Haematopoietic stem cell transplantation as well as the recently introduced chimeric antigen receptor (CAR)-T-cell therapy are innovative therapies to produce a cure in a subset of patients with haematological malignancies. However, coagulopathy frequently occurs after these therapies, which limits the success of the treatment. For example, DIC is noted in approximately 50% of patients after CAT-T-cell therapy in conjunction with cytokine release syndrome. Hematopoietic stem cell transplantation (HSCT) causes endotheliitis, which triggers coagulopathy and the development of potentially lethal complications, such as sinusoidal obstruction syndrome/veno-occlusive disease and transplant-associated thrombotic microangiopathy. This review article describes the pathogenesis, clinical manifestation, diagnosis, and treatment of DIC caused by haematological malignancies, CAR-T-cell therapy, and HSCT.

Keywords DIC · Haematological malignancies · APL · VOD/SOS · TA-TMA · Cytokine release syndrome

Introduction

Disseminated intravascular coagulation (DIC) is an acquired thrombotic disorder that is caused by various underlying diseases, with sepsis being the leading cause, followed by shock, solid cancer, and haematological malignancies, including non-Hodgkin lymphoma and acute leukaemia [1, 2]. The disease that is most frequently accompanied by DIC is acute promyelocytic leukaemia (APL); nearly 70% of newly diagnosed APL patients develop DIC [3]. Approximately 17% and 11% of non-APL acute myeloid leukaemia (AML) and non-Hodgkin lymphoma patients, respectively, develop DIC at the time of diagnosis [4, 5]. The prognosis of patients with haematological malignancies is exacerbated by concomitant DIC. It is not clear whether early diagnosis of DIC and initiation of treatment for this thrombotic disorder improve the prognosis of patients because of the paucity of prospective clinical trials.

Haematopoietic stem cell transplantation (HSCT) is an innovative treatment strategy to cure haematological malignancies as well as bone marrow failure syndromes such as aplastic anaemia. However, transplant-associated thrombotic complications such as sinusoidal obstruction syndrome/veno-occlusive disease (SOS/VOD) and transplant-associated thrombotic microangiopathy (TA-TMA) are barriers to the success of HSCT [6, 7]. Vascular endothelial cell (VEC) damage is one of the key factors that triggers the development of these potentially lethal complications. In

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association with VEC damage, coagulopathy is frequently noted in patients with SOS/VOD and transplant-associated TMA (TA-TMA) [6].

Recently introduced chimeric antigen receptor (CAR)-T-cell therapy also produces a cure in a subset of patients with relapsed/refractory B-cell malignancies. Given that cytokine release syndrome frequently occurs after CAR-T-cell therapy, it is understandable that the development of DIC is noted in approximately half of patients.

This review article describes the pathogenesis, clinical manifestation, diagnosis, and treatment of DIC caused by haematological malignancies, CAR-T-cell therapy, and HSCT.

The pathogenesis of DIC caused by haematological malignancies

(1) Procoagulant activity

Hypercoagulability is present in patients with haematological malignancy-associated DIC, as an increase in plasma levels of coagulation markers such as the thrombin–antithrombin complex (TAT) and soluble fibrin monomer (SF) are noted in these patients [5, 8–11]. Leukaemia cells aberrantly express tissue factor (TF), which interacts with factor VII and orchestrates the extrinsic coagulation cascade, leading to the production of thrombin, which converts fibrinogen to fibrin, causing fibrin deposition [3]. In cases of malignant lymphoma (ML), the expression levels of TF on the cell surface of lymphoma cells are relatively low; however, immunohistochemistry analysis found that vascular endothelial cells surrounding the lymphoma tissue aberrantly express TF, which may contribute to the hypercoagulable state in lymphoma patients [12]. Acute leukaemia and lymphoma cells aberrantly express inflammatory cytokines such as interleukin-6 (IL-6) and tumour necrosis factor-α (TNF-α), which cause vascular endothelial cell damage, resulting in an increase in the expression of TF and plasminogen activator inhibitor 1 (PAI-1) in parallel with a decrease in the expression of thrombomodulin (TM), which converts protein C to activated protein C (APC) and inhibits coagulation. APL and non-APL AML cells release many microparticles (MPs) harbouring TF and cancer procoagulant (CP), which has serine protease activity, directly activates factor X (FX), and generates thrombin (Fig. 1) [13, 14].

Another mechanism by which haematological malignant cells cause hypercoagulability revolves around intranuclear proteins such as HMGB1 (high-mobility group box-1) and histones. HMGB1 plays a critical role in the pathogenesis of sepsis-induced DIC; HMGB1 released from the nuclei of pathogen-activated macrophages further stimulates inflammation by binding to Toll-like receptor 2/4 (TLR2/4) and/or receptor for advanced glycation end products expressed on the cell surface of immune cells. In addition, HMGB1 enhances thrombin-mediated fibrin formation [15, 16]. The nuclear extracellular traps (NETs) released from pathogen-activated neutrophils interact with factor XII and orchestrate the intrinsic coagulation cascade. Histones, especially histone H3 and H4, are the main components of NETs and were shown to cause vascular endothelial cell damage and coagulopathy in in vivo experiments [17–20]. Additionally, histones activate platelets by binding to TLR2/4 and promote thrombin generation by platelets [21]. Recent studies found that serum levels of both HMGB1 and histone H3 were increased in patients with acute leukaemia complicated by DIC compared to those without DIC [22]. The levels of these intranuclear proteins were correlated with the DIC score. These observations suggest that intranuclear proteins liberated from the nuclei of leukaemia cells play a role in the development of DIC.

(2) Activation of fibrinolysis

In physiological conditions, the fibrinolytic system is activated following thrombin formation to degrade fibrin deposition and avoid peripheral circulatory insufficiency; however, this system is hampered by cytokine-induced expression of PAI-1, which inhibits plasminogen activator-mediated plasmin production in sepsis-induced DIC patients [23]. Thus, organ failure associated with circulatory insufficiency is a typical clinical manifestation of sepsis-induced DIC. Plasma levels of PAI-1 were correlated with the severity of sepsis and were able to predict the mortality of patients [24]. On the other hand, this fibrin-induced fibrinolytic process, the so-called secondary fibrinolysis, is not blunted in haematological malignancy-associated DIC. Additionally, primary fibrinolysis is extremely activated in AML-associated DIC, especially in APL-associated DIC. Thus, marked hypofibrinogenemia and an increase in the ratio of fibrin/fibrinogen degradation products (FDPs), D-dimer levels, and the plasmin/α-2-antiplasmin complex (PIC) are noted in APL patients [3]. Several possible factors play a role in the development of hyperfibrinolysis in APL patients. Among many, the annexin II/A100S10 heterotetrameric complex expressed on the surface of APL cells is a major player [25, 26]. The gene expression of the complex components is intimately regulated by *PML/RARα*, a hallmark gene alteration in APL [27]. Annexin II after binding to S100A10 prevents this Ca^{2+}-binding protein from ubiquitination-dependent protein degradation. S100A10 possesses lysin residues in its C-terminus, which act as the cell surface receptors for both plasminogen and tissue-type-plasminogen activator (t-PA) [28]. Thus, plasmin is effectively generated on the cell surface of APL cells (Fig. 2). The annexin/S100A10 heterotetramer is

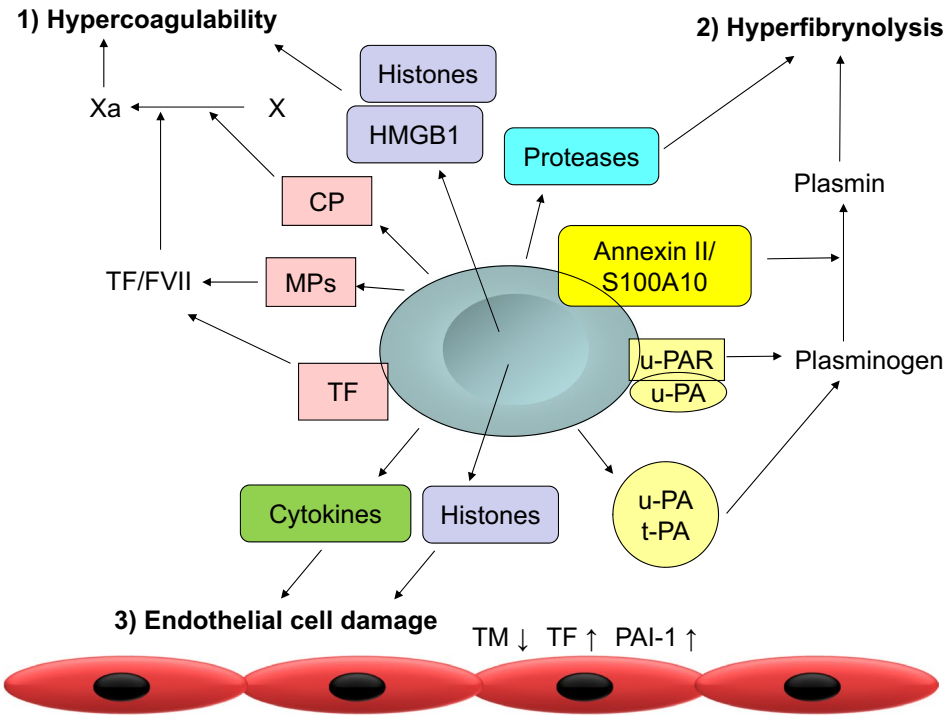

Fig. 1 APL cells cause both hypercoagulability and hyperfibrinolysis. (1) Hypercoagulability. APL cells produce TF, CP, and MPs, which activate the coagulation cascade. Additionally, APL cells release histones and HMGB1 from their nuclei, which activate coagulation cascades. (2) Hyperfibrinolysis. APL cells produce t-PA, u-PA, and u-PAR, which activate plasminogen. APL cells aberrantly express the annexin II/A100S10 heterotetramer on their cell surface, which mediates the conversion of plasminogen to plasmin. Elastases produced by APL cells may cleave fibrinogen and degrade fibrinolytic inhibitors, resulting in hyperfibrinolysis. (3) Endothelial cell damage. APL cells produce inflammatory cytokines, including IL-1β, IL-6, and TNF-α, all of which cause endothelial cell damage and downregulate the expression of TM in parallel with the upregulation of TF and PAI-1 on the cell surface of endothelial cells, resulting in hypercoagulability. Histones released from APL cells also cause endothelial damage. *TF* tissue factor, *CP* cancer procoagulant, *MPs* microparticles, *t-PA* tissue-type-plasminogen activator, *u-PA* urokinase-type-plasminogen activator, *u-PAR* u-PA receptor, *IL-1β* interleukin-1β, *IL-6* interleukin-6, *TNF-α* tumour necrosis factor-α, *TM* thrombomodulin, *PAI-1* plasminogen activator inhibitor-1, *HMGB1* high-mobility group box 1. This figure is adapted from Ref. [5]

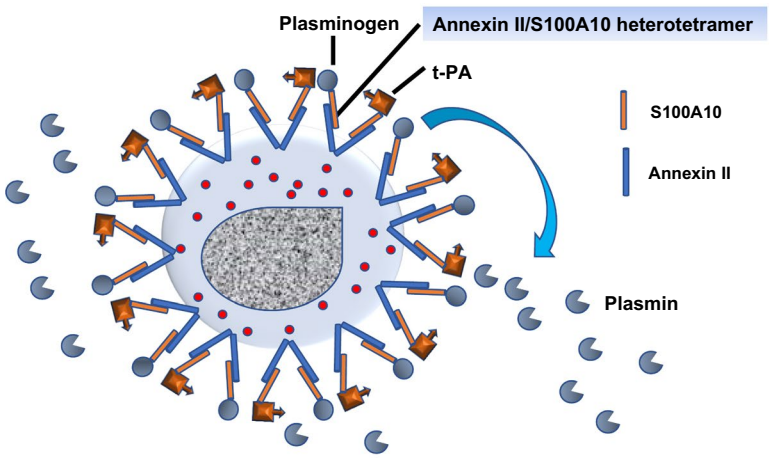

Fig. 2 Annexin II/S100A10 heterotetramer mediates plasmin production. Annexin II and S100A10 form a heterotetramer complex on the surface of APL cells. Both tissue plasminogen activator and plasminogen possess a high affinity for the lysin residues in the C-terminus of S100A10, thereby effectively producing plasmin. *APL* acute promyelocytic leukaemia, *t-PA* tissue plasminogen activator. This figure is adapted from Ref. [26]

also expressed on vascular endothelial cells. Other molecules expressed by APL cells and that generate plasminogen include t-PA, urokinase-type PA (u-PA), and its receptor, u-PA receptor (Fig. 1) [29–31].

(3) Tumour lysis and DIC

Approximately 15% of non-APL AML patients develop DIC soon after the initiation of remission induction chemotherapy [4], suggesting that coagulopathy is exacerbated as malignant cells undergo apoptosis after exposure to cytotoxic agents and/or molecular targeting agents, such as rituximab for CD20 antigen-positive lymphoma. Recent studies have identified a possible link between intranuclear proteins such as histone H3 and HMGB1 released from leukaemia cells and the development of tumour lysis-associated DIC [22]; an increase in plasma levels of these prothrombotic intranuclear proteins was noted after initiation of remission induction chemotherapy, which was followed by an increase in levels of FDP and D-dimer and diagnosis of DIC. These observations suggest that intranuclear proteins liberated from the nuclei of leukaemia cells undergoing apoptosis trigger coagulopathy. Other factors involved in tumour lysis-associated DIC include extracellular vesicles (EVs) and phosphatidylserine (PS). An in vitro study found that exposure of acute lymphoblastic leukaemia (ALL) cells to vincristine but not daunorubicin caused a release of EVs possessing prothrombotic activity from ALL cells and externalization of PS on their cell surface, where the activation of coagulation cascades is magnified (Fig. 3) [32]. Additionally, exposure of AML cells to daunorubicin enhanced the production of TF and its prothrombotic activity in these cells [33, 34].

Clinical manifestations of DIC caused by AML

The development of DIC in non-APL AML patients is associated with an increase in white blood cell (WBC) counts, an elevation of C-reactive protein (CRP), depletion of the cell surface antigens CD13 and HLA-DR, a normal karyotype, and the 11q23 chromosomal abnormality [4]. One clinical manifestation of APL is fatal haemorrhage. Approximately 5% of APL patients died of fatal haemorrhage, including intracranial or alveolar haemorrhage, within the first week after initiation of remission induction chemotherapy with idarubicin in combination with all-*trans*-retinoic acid (ATRA) in a clinical trial setting [35, 36]. The presence of DIC and increased WBC counts ($>30\times10^9$/L) and creatinine levels was identified as a factor predicting fatal haemorrhage [35]. Kim et al. retrospectively analysed risk factors for fatal intracranial haemorrhage in 792 patients with AML and ALL. The multivariate analysis found that female sex (relative risk (RR) = 5.234), APL (RR = 4.057), leukocytosis (RR = 3.301), thrombocytopenia (RR = 3.283), and prolonged prothrombin time (RR = 3.291) were significantly associated with the development of fatal intracranial haemorrhage [37]. A Japanese group also found that a combination of hyperleukocytosis ($>50\times10^9$/L) and elevated plasma levels of FDP (>40 μg/mL) was a predictive marker for fatal intracranial haemorrhage in acute leukaemia [38].

Importantly, 11 out of 124 APL patients (8.9%) developed thrombotic events, including myocardial infarction and deep venous thrombosis, following the initiation of remission induction chemotherapy with idarubicin and ATRA. Hyperleukocytosis and the presence of the CD2 and CD15 cell surface antigens, bcr3 type PML/RARα transcripts, and *FLT3–ITD* mutation was recognized as a predictive

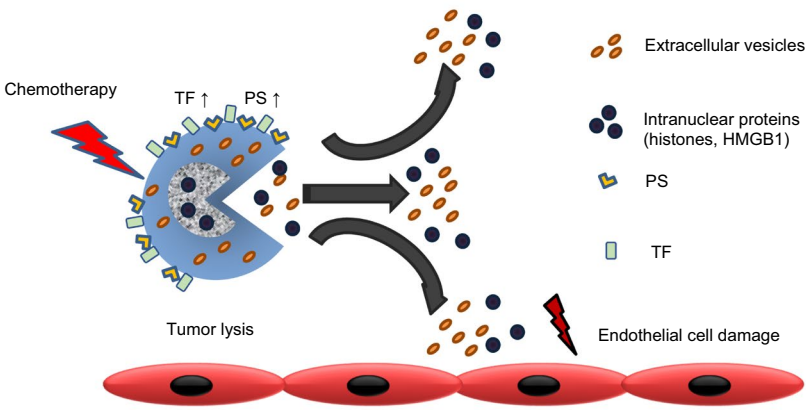

Fig. 3 Tumour lysis-associated DIC. Exposure of leukaemia cells to anti-leukaemia agents causes expression of TF and release of EVs and intranuclear proteins histones and HMGB1, which stimulate thrombin generation. Histones also cause vascular endothelial cell damage, resulting in hypercoagulability. Additionally, PS is externalized on the surface of leukaemia cells, where the activation of the coagulation cascades is boosted. *EVs* extracellular vesicles, *HMGB1* high-mobility group box 1, *TF* tissue factor, *PS* phosphatidylserine

marker of thrombotic events in APL patients [39]. The use of ATRA promptly normalizes the D-dimer level, suggesting the inhibition of fibrinolysis; however, normalization of F1 + 2 and TAT, a marker of hypercoagulability, is delayed [8]. Exposure of APL cells to ATRA produces inflammatory cytokines associated with myeloid differentiation, which causes endothelial cell damage [40]. Thus, alteration of the balance between coagulation and fibrinolysis and endothelial cell damage caused by ATRA may contribute to thrombotic events in APL patients receiving ATRA. Of note, some APL patients died of fatal thrombotic complications while receiving ATRA in combination with an anti-fibrinolysis agent tranexamic acid [41, 42]. Thus, this combination therapy should be avoided in APL patients.

Diagnosis of DIC caused by haematological malignancy

The use of diagnostic criteria released by the Japanese Society on Thrombosis and Hemostasis (JSTH) in 2017 is recommended to diagnose haematological malignancy-associated DIC [43]. This set of criteria features updates to the set established by the Ministry of Health and Welfare in 1988, including the addition of new evaluation factors such as AT, SF, and TAT. The efficacy of the new DIC diagnostic criteria for predicting the survival of patients with DIC caused by various types of underlying diseases is currently being evaluated by the DIC Committee of JSTH (UMIN000032972).

Treatment of DIC caused by haematological malignancy

Heparinoids, including low-molecular-weight heparin (LMWH) and unfractionated heparin (UFH), synthetic serine protease inhibitors, antithrombin products, and recombinant human soluble thrombomodulin (rTM), are approved for the treatment of DIC in Japan. The levels of AT remain within the normal range in most cases of DIC caused by haematological malignancies except for malignant lymphoma (ML) [5, 44]. In one study, all malignant lymphoma patients with DIC ($n = 18$) were at an advanced clinical stage with bone marrow involvement [5]. Low levels of AT together with hypoalbuminemia and a decrease in choline esterase levels were noted in these patients, suggesting that low levels of AT were probably associated with an impairment of production in the liver. Notably, AT activity under 80% was a predictive marker of poor prognosis of ML patients [5]. There is no clinical trial evaluating whether the replacement of AT would improve the survival of ML patients.

A questionnaire-based survey found that rTM is the most frequently used anticoagulant to treat DIC caused by acute leukaemia in Japan, with synthetic serine protease inhibitors being the second most frequently used [45]. rTM comprises the extracellular domains of TM, which is mainly expressed on vascular endothelial cells and negatively regulates coagulation by binding thrombin

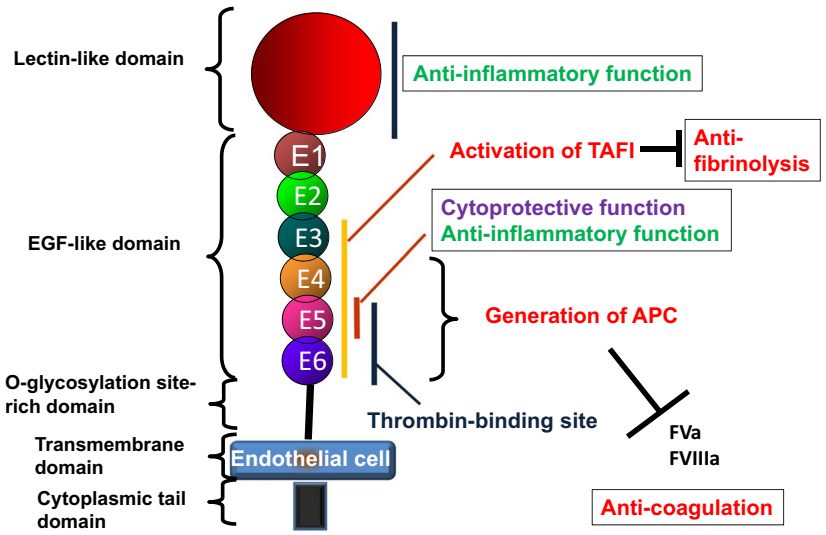

Fig. 4 The structure and function of TM. After binding to thrombin, TM generates APC and activated forms of TAFI that inhibit coagulation and fibrinolysis, respectively. The lectin-like domain of TM exerts its anti-inflammatory function. The fifth region of the EGF-like domain (E5) exerts both cytoprotective and anti-inflammatory functions. *TM* thrombomodulin, *EGF* epidermal growth factor, *TAFI* thrombin-activatable fibrinolysis inhibitor, *APC* activated protein C, *FVa* activated factor V, *FVIIIa* activated factor VIII, *rTM* recombinant human soluble thrombomodulin. This figure is adapted from Ref. [3]

via the fourth and fifth regions of its epidermal growth factor (EGF)-like domain (Fig. 4). Additionally, upon binding to thrombin, TM converts protein C to APC, which inhibits further thrombin formation via inhibition of activated factors V and VIII [46]. Intriguingly, TM also inhibits fibrinolysis; after interacting with thrombin, TM converts carboxypeptidase thrombin-activatable fibrinolysis inhibitor (TAFI) to activated TAFI (TAFIa), which removes the lysine residues on fibrin to which both t-PA and plasminogen bind, thereby inhibiting plasmin production [47]. Notably, the *N*-terminal lectin-like domain of TM exerts anti-inflammatory activities by binding and degrading HMGB1, which is released from apoptotic cells and activated macrophages, and stimulates the production of inflammatory cytokines via TLR4 and receptor for advanced glycation end products [48]. Furthermore, the fifth domain of the epidermal growth factor (EGF)-like region of TM (TME5) possesses both a cytoprotective function for vascular endothelial cells and an anti-inflammatory function. TME5, after interacting with the cell surface-expressed chemokine receptor G protein-coupled receptor 15 (GPR15), mediates the pro-survival signalling pathway, upregulates the anti-apoptotic protein Mcl-1 in VECs, and protects these cells from injury caused by cytokines [49, 50]. TME5 rescued mice from LPS-induced sepsis in association with a decrease in the production of cytokines [51]. TME5 also alleviated graft-versus-host disease (GVHD) in a murine model in association with inhibition of alloreactivity [52]. rTM comprises extracellular domains of TM and possesses all of these functions. A phase 3 clinical trial comparing the efficacy and safety between rTM and unfractionated heparin in patients with DIC caused by haematological malignancy or infection found that the use of rTM had merit in DIC resolution and the disappearance of bleeding symptoms [53]. Based on the results of this clinical trial, rTM was approved as an anti-DIC agent in Japan in 2008. Post-market surveillance confirmed the efficacy and safety of rTM in patients with DIC associated with non-APL AML ($n = 350$), ML ($n = 199$), APL ($n = 172$), ALL ($n = 156$), myelodysplastic syndrome ($n = 61$), and other diseases ($n = 94$) [44, 54]. Earlier DIC resolution and a higher rate of DIC resolution were noted in APL-related DIC patients treated with rTM than in those treated with low-molecular-weight heparin or a synthetic serine protease inhibitor [55, 56]. Of note, the use of rTM did not exacerbate bleeding symptoms in APL patients, supporting the relative safety profile of this agent. The in vitro study showed that exposure of APL cells to rTM in combination with ATRA significantly enhanced ATRA-mediated downregulation of annexin II and decreased the production of plasmin in these cells [57]. Interestingly, a retrospective analysis found that the use of rTM significantly improved the overall survival of AML patients compared with the use of LMWH [58]. A prospective clinical trial is warranted to compare the efficacy and safety between rTM and other anticoagulants, such as LMWH and synthetic serine protease inhibitors.

Clinical trials comparing the efficacy and safety of synthetic serine protease inhibitors with those of placebo or other anticoagulants in haematological malignancy-associated DIC patients are limited. Only one study retrospectively compared the efficacy of two different types of synthetic serine protease inhibitors, gabexate mesylate (FOY) and nafamostat (FUT), in patients with haematological malignancies ($n = 127$) and found comparable efficacy, with a DIC resolution rate at day 7 of 40–45% [59]. Improvement of the underlying haematological disease correlated with DIC resolution.

DIC associated with CAR-T-cell therapy

Chimeric antigen receptor (CAR)-T-cell therapy is an innovative strategy for relapsed/refractory (R/R) haematological malignancies [60]. CAR-T-cell therapy targeting CD19, CD20, or B-cell maturation antigen produced durable remission in patients with R/R ALL, non-Hodgkin lymphoma, and multiple myeloma. On the other hand, approximately 50% of patients who received CAR-T-cell therapy developed life-threatening cytokine release syndrome (CRS) of any grade [61]. Recently, Chinese groups have reported that approximately 50% of patients developed coagulopathy within 28 days after CAR-T-cell infusion [62, 63]. Thirteen percent of these patients met the DIC diagnostic criteria released by the International Society on Thrombosis and Haemostasis [64]. The laboratory findings of DIC following CAR-T-cell therapy include hypofibrinogenemia, thrombocytopenia, an increase in plasma levels of FDP and D-dimer, and prolongation of prothrombin time (PT) and activated partial thromboplastin time (APTT), suggesting the enhanced fibrinolysis [62, 63]. The only clinical manifestation of DIC following CAR-T-cell therapy was bleeding. Clinically significant bleeding was noted in 10 out of 51 (19.6%) patients with coagulopathy, which included fatal intracranial haemorrhage [62]. The development of DIC was correlated with the incidence and severity of CRS and serum levels of IL-6, suggesting the involvement of cytokine storm in the pathogenesis of DIC [63].

DIC associated with HSCT

Nearly 60% of patients who received HSCT for haematological malignancies developed coagulopathy of any grade between the day when the preparative regimen was initiated and day 35 after transplantation [65]. The most common

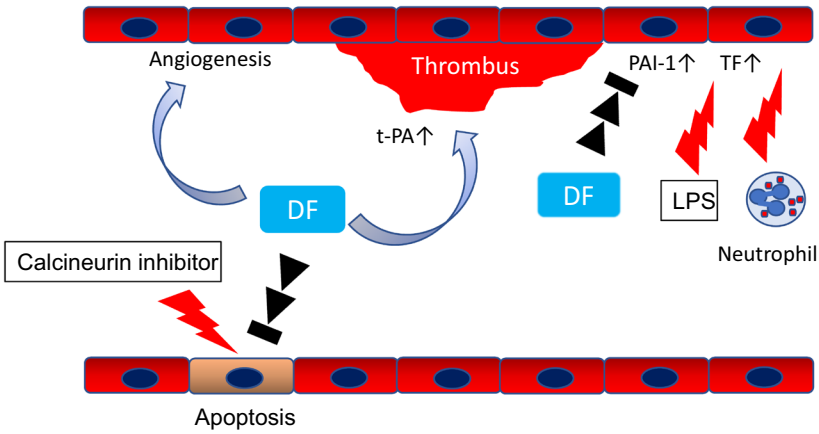

Fig. 5 The mode of action of DF. DF counteracts LPS and cathepsin-G released from neutrophils, which normally induce the expression of PAI-1 and TF in vascular endothelial cells. In contrast, DF induces the production of t-PA. DF blocks calcineurin inhibitor-induced apoptosis of vascular endothelial cells. DF induces angiogenesis. *DF* defibrotide, *PAI-1* plasminogen activator inhibitor 1, *LPS* lipopolysaccharide, *TF* tissue factor, *t-PA* tissue plasminogen activator

underlying conditions that caused coagulopathy included infection and engraftment syndrome followed by TA-TMA, SOS/VOD, and acute GVHD (aGVHD). The retrospective analysis found that the prognosis of HSCT-treated patients who developed coagulopathy, as evidenced by an increase in the levels of D-dimer, TAT, SF, and PAI-1 within 4 weeks of HSCT, was worse than that of those without coagulopathy [66]. Intriguingly, the use of rTM for coagulopathy significantly improved the survival rate at day 100 after HSCT and prolonged overall survival compared with no use of rTM, although these findings are from a retrospective study at a single institution [65].

(1) VOD/SOS and DIC

Various factors, including the use of high-dose busulfan and total body irradiation as a preparative regimen and calcineurin inhibitors for GVHD prophylaxis, cause systemic vascular endothelial cell damage, resulting in the derangement of their function. In particular, hepatic sinusoidal endothelial cells (HSECs) in zone three of the liver, where the amount of glutathione with detoxification activity is low, are the main targets of toxic agents in the onset of VOD/SOS [6, 7, 67]. The cell-to-cell junction is disrupted after HSECs are injured, which allows red blood cells to penetrate into the space of Disse beneath the HSECs, resulting in a misalignment of HSECs [6, 7, 68]. As a result, the blood flow is disturbed, and thrombotic embolization eventually occurs. The clinical features of VOD/SOS comprise jaundice, hepatomegaly with tenderness, and body weight gain [67]. Additionally, transfusion-refractory thrombocytopenia is frequently noted after the diagnosis of VOD/SOS [69]. As a consequence of VEC damage, mild-to-moderate coagulopathy occurs, and some cases meet the diagnostic criteria of DIC [65]. Several case reports show the efficacy of rTM in VOD/SOS patients with coagulopathy [70–73]. A questionnaire-based survey found that 41 VOD/SOS patients were treated with rTM in Japan, with a resolution rate at day 100 of 54% [74]. TM5E prevented VOD/SOS in a murine model without bleeding-related toxicities [75, 76].

Defibrotide (DF), a mixture of single-stranded phosphodiester oligonucleotides, is the only agent that is approved for the treatment of VOD/SOS. A systematic review of 17 clinical trials found that the survival rate of patients with or without multi-organ failure at day 100 after HSCT was 44 or 71%, respectively [77]. The molecular mechanisms by which DF produces beneficial effects on VOD/SOS remain to be fully elucidated; however, several publications suggest the anti-thrombotic function of DF. For example, an in vitro study showed that DF hampered the platelet activation mediated by cathepsin-G released from neutrophils (Fig. 5) [78]. Administration of DF attenuated thrombin-induced thromboembolism in rabbits [79]. Exposure of VECs to DF counteracted LPS-induced expression of PAI-1 and TF in parallel with an increase in the expression of t-PA, suggesting the pro-fibrinolytic activity of DF [80]. Moreover, an increase in plasma levels of t-PA was noted in healthy individuals after receipt of DF [81]. Furthermore, DF possesses angiogenic activity and protects VECs from calcineurin inhibitor-mediated apoptosis in association with an increase in the levels of the anti-apoptotic protein Bcl-xL [82].

(2) TA-TMA and DIC

TA-TMA develops at median days 30–50 after HSCT with an incident rate of 15–30% in HSCT [83]. The pathophysiology of TA-TMA differs from that of thrombotic thrombocytopenic purpura (TTP), a typical type of TMA in which extremely low levels (< 10%) of a disintegrin-like and metalloproteinase with thrombospondin-type 1 motifs 13 (ADAMTS13) play a critical role. The two-hit theory is advocated for the pathogenesis of TA-TMA; the first hit comprises many risk factors, including preparative regimens with high-dose busulfan and TBI, which cause endothelial injury, leading to a prothrombotic state. The second hit, such as acute GVHD or infection, facilitates endothelial injury,

resulting in the initiation of thrombus formation and the development of TA-TMA [83]. The most affected organ in TA-TMA is the kidney, followed by the gastrointestinal tract and lungs. As a consequence of endothelial injury, coagulation abnormalities in association with an increase in the levels of soluble TM, von Willebrand factor antigen, and PAI-1 were noted in patients with TA-TMA [84, 85]. Pathological examination found the deposition of complement factors in kidneys biopsied from TA-TMA patients, and these findings are comparable with those of atypical haemolytic uremic syndrome (aHUS), in which dysregulated complement plays a pathophysiological role [86, 87]. Additionally, recent studies utilizing the transcriptome found that the classical, alternative, and lectin complement pathways are activated in peripheral blood mononuclear cells isolated from patients with TA-TMA. Interestingly, these complement-activated signatures disappeared when TA-TMA was improved by the anti-human C5 antibody eculizumab [88]. Moreover, Jodele et al. found that the C5b-9 complex, a marker of terminal complement activation, was elevated in serum isolated from TA-TMA patients, and this level was correlated with poor prognosis. The authors also found that proteinuria ($\geq$30 mg/dL), hypertension, and an increase in lactate dehydrogenase occurred 10–14 days before the diagnosis of TA-TMA was made, suggesting that these parameters can be an early diagnostic marker [89]. The complement components activate platelets and coagulation cascades, leading to thrombus formation [90–92].

The prognosis of TA-TMA is dismal because of the lack of established treatment strategies. The use of agents with endothelial protective function might be a promising strategy. A questionnaire survey found that DF was used for 39 patients with TA-TMA and resulted in a remission rate of 77% [93]. The use of rTM also significantly improved the prognosis of TA-TMA patients compared with no use of rTM, although the results are from a retrospective analysis performed at a single institution [94]. Another promising agent to treat TA-TMA is a monoclonal antibody targeting the complement system. A clinical trial to evaluate the efficacy and safety of this anti-complement antibody is needed.

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Compliance with ethical standards

Conflict of interest Ikezoe T receives a research fund form Asahi Kasei Pharma and Nihon Shinyaku Co., Ltd.

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