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PROGRESS IN HEMATOLOGY

DIC Clinical Practice Guidelines 2024

Clinical practice guidelines for management of disseminated intravascular coagulation in Japan 2024. Part 2: hematologic malignancy

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Abstract
Disseminated intravascular coagulation (DIC) associated with hematologic malignancies, particularly acute promyelocytic leukemia (APL), is characterized by marked fibrinolytic activation, which leads to severe bleeding complications. Therefore, appropriate diagnosis and management of DIC are crucial for preventing bleeding-related mortality. However, to date, no clinical guidelines have specifically addressed hematologic malignancy-associated DIC. Therefore, we developed diagnostic and management algorithms for DIC based on a systematic literature review. Notably, these guidelines recommend using the JSTH DIC diagnostic criteria (2017 version) or the former Ministry of Health and Welfare DIC diagnostic criteria (1983 version) to diagnose DIC. Furthermore, in the management of DIC, it is essential to treat the underlying disease through transfusion of platelet concentrates and fresh frozen plasma, if necessary. A systematic review of antifibrinolytic and anticoagulant therapies concluded that tranexamic acid therapy is not strongly recommended for patients with APL undergoing treatment with all-trans retinoic acid (Grade 1C). The use of recombinant thrombomodulin is weakly recommended (Grade 2B), whereas the use of other anticoagulants, including heparin and serine protease inhibitors, is weakly not recommended (Grade 2C). Therefore, we hope that these guidelines will help physicians find the best possible solutions in clinical practice.

Keywords DIC · Hematologic malignancy · Diagnostic criteria for DIC · Replacement therapy · Anticoagulation therapy

Introduction

Disseminated intravascular coagulation (DIC) associated with hematologic malignancies, particularly acute promyelocytic leukemia (APL), is a serious clinical condition characterized by an increased incidence of bleeding-related deaths, especially in the early phases of chemotherapy [1–3], and poor prognosis [4–6]. Population-based studies on APL in Japan and abroad (Sweden, USA, and Brazil) have shown that early bleeding-related deaths (within 28 days of starting chemotherapy) remain significantly high, ranging from 5 to 20% [7–10].

Clinical manifestations of DIC in patients with hematologic malignancies are associated with concomitant hypercoagulable states and hyperfibrinolysis. The hypercoagulable state results from increased production of tissue factors and cancer procoagulants by leukemic cells [1–3]. However, hyperfibrinolysis is associated with cell-surface-expressed annexin II/S100A10 complexes, which catalyze excessive plasmin production [1–3], leading to marked fibrinolytic-type DIC that often presents with hemorrhagic symptoms [1–3].

In Japan, several anticoagulants are available for managing DIC, including recombinant thrombomodulin,

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antithrombin (AT), serine protease inhibitors, and heparin. However, the benefits of therapeutic intervention for DIC, as opposed to managing the underlying disease and providing replacement therapy, remain unclear. Furthermore, the optimal anticoagulant for the treatment of DIC associated with hematological malignancies remains unclear.

Antifibrinolytic agents, such as tranexamic acid (TA), may offer potential benefits in hyperfibrinolytic-type DIC by inhibiting plasmin production. However, there is concern that these agents may increase the risk of fatal thrombosis, given the concurrent hypercoagulable state that exists even in patients with hyperfibrinolytic-type DIC.

Based on these circumstances, evidence-based practice guidelines for DIC are required to assist physicians in the appropriate diagnosis and management of DIC associated with hematological malignancies.

The primary objective of this guideline is to provide a comprehensive overview of the diagnosis of DIC, replacement therapy with platelet concentrates (PCs) and fresh frozen plasma (FFP), and the benefits and harms of each treatment, and support clinical decision-making and improve patient outcomes in the management of DIC associated with hematological malignancies in clinical practice.

These guidelines were developed through a structured process that included defining the scope, formulating clinical questions, conducting a literature search, performing systematic reviews, and issuing recommendations. The methodology for developing these guidelines has also been described in the sepsis-related section of the DIC Clinical Practice Guidelines 2024.

Treatment strategies and recommendations for DIC

Figure 1 shows the algorithm for the diagnosis and treatment of DIC associated with hematological malignancies. DIC associated with hematologic malignancies is a pathologic condition characterized by increased fibrinolytic conditions and coagulation activation, rendering patients particularly prone to bleeding. Notably, DIC is a significant risk factor for premature death due to severe hemorrhage. Thus, appropriate diagnosis and targeted treatment of DIC may be crucial for mitigating severe bleeding. First, it is essential to understand which types of hematological malignancies are more frequently associated with DIC (Question 1). Second, using appropriate diagnostic criteria when DIC is suspected is crucial (Question 2). However, once DIC is diagnosed, the subsequent treatment is critical. Notably, treatment should focus primarily on addressing the underlying malignancy. In addition, adjunctive therapies, including blood transfusion, fibrinolytic therapy, and anticoagulation, may be incorporated into the overall treatment strategy. Furthermore, a systematic review was conducted for each drug currently available in Japan, including antifibrinolytic therapy (Question 3), recombinant thrombomodulin (Question 4), heparin (Question 5), serine protease inhibitors (Question 6), and

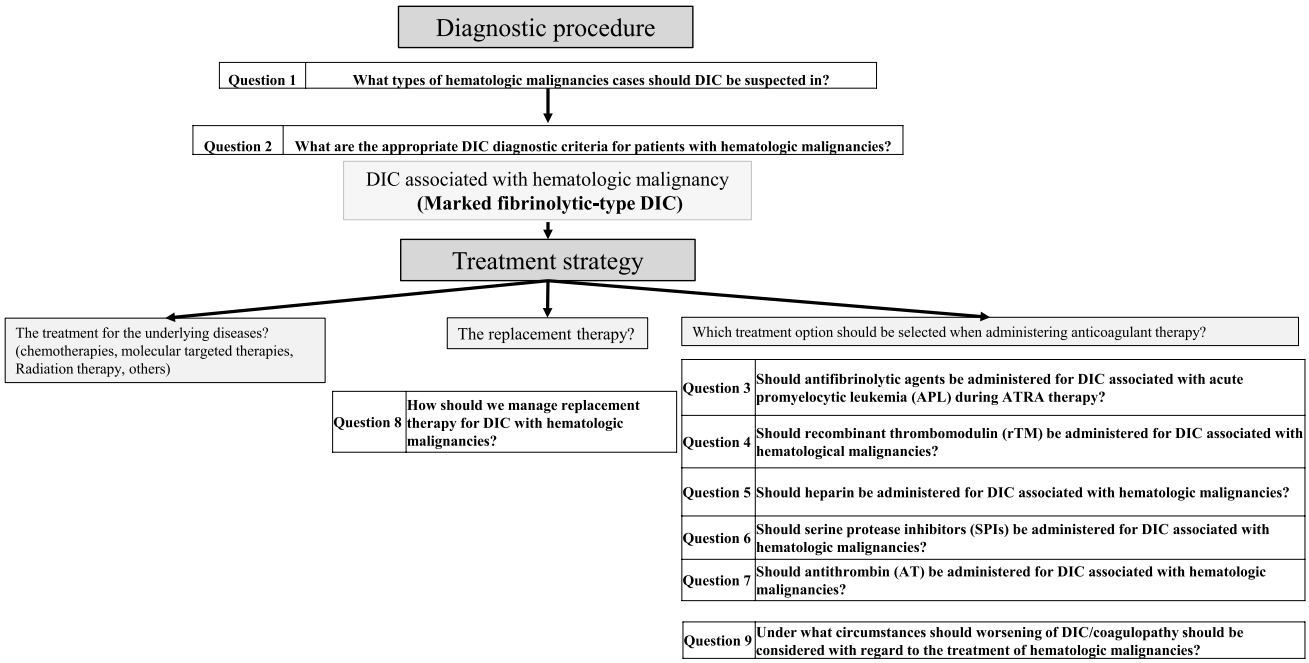

Fig. 1 A current algorithm of diagnosis and treatment of DIC associated with hematologic malignancy

AT (Question 7). The potential benefits and harms of each intervention were carefully evaluated, and the strength of the recommendations was determined accordingly. For replacement therapy, our statement was to manage blood transfusions based on the clinical guidelines currently published by other academic societies in Japan and abroad (Question 8). Furthermore, we addressed the unique clinical situation of worsening coagulopathy during the treatment of hematologic malignancies in Question 9. The questions and corresponding recommendations are summarized in Table 1.

Question 1 (BQ): What types of hematologic malignancies cases should DIC be suspected in?

Statement

Patients with acute leukemia, advanced-stage malignant lymphoma or hemophagocytic syndrome complicated by malignant lymphoma are more susceptible to DIC.

Explanation

Hematological malignancies account for several underlying diseases associated with DIC. Notably, even if DIC is not present at the time of diagnosis of a hematologic malignancy, it may develop later owing to tumor lysis triggered by subsequent chemotherapy. Therefore, ensuring the accurate diagnosis and appropriate management of DIC is essential for the safe administration of chemotherapeutic treatments.

Among hematologic malignancies, APL has the highest association with DIC, with a reported complication rate of approximately 60% [11, 12]. In contrast, the incidence of DIC in patients with acute myeloid leukemia (AML), excluding APL, is estimated to be 16–18%. Risk factors for developing DIC in patients with AML include high white blood cell count, M5 subtype in the French–American–British classification, 11q23 chromosomal abnormalities, and concurrent infections [13, 14]. The incidence of DIC at the time of diagnosis in patients with acute lymphoblastic leukemia is reported to range from 10 to 20% [15, 16].

The incidence of DIC in patients with malignant lymphoma ranges from 3 to 11.2% [15, 16]. Advanced-stage disease, particularly bone marrow infiltration, is associated with a higher frequency of DIC complications. Notably, some studies have suggested no significant differences in the incidence of DIC based on lymphoma histology [15]. However, others have reported a higher frequency of Natural killer (NK)/T-cell lymphoma [16]. DIC frequently complicates lymphoma-associated hemophagocytic syndrome (LAHS). An observational study of 29 patients with LAHS showed that none of the five patients with B-cell lymphoma had DIC, whereas 16 of the 24 patients complicated with LAHS associated with T-cell or NK/T-cell lymphoma developed DIC [17]. Chronic active Epstein–Barr virus infection may also be associated with hemophagocytic syndrome and DIC [18]. The incidence of DIC in patients with multiple myeloma (MM) is unclear; however, there have been case reports of plasma cell leukemia complicated by DIC [19]. AL amyloidosis is associated with an increased risk of fibrinolytic-type DIC [20].

Question 2 (BQ): What are the appropriate DIC diagnostic criteria for patients with hematologic malignancies?

Statement

Diagnoses are made according to the DIC diagnostic criteria of the Japan Society for Thrombosis and Hemostasis (JSTH) (2017 version) or the DIC diagnostic criteria of the former Ministry of Health and Welfare (MHW) (1983 version).

Explanation

Accurate diagnosis of DIC and appropriate therapeutic intervention are crucial for the effective treatment of underlying hematologic malignancies. Notably, several DIC diagnostic criteria have been published in Japan and other countries; however, no study has directly compared the diagnostic accuracy of DIC associated with hematologic malignancies across these criteria. Therefore, the superiority or inferiority of the specific diagnostic criteria for DIC remains unclear.

In Japan, the former MHW diagnostic criteria (1983) are commonly used in DIC research. However, the International Society on Thrombosis and Hemostasis (ISTH) diagnostic criteria (2001 version) are more frequently used in international studies.

Notably, both diagnostic criteria included fibrin degradation products (FDP), fibrinogen, and prothrombin time (PT) as critical diagnostic markers. However, a notable difference is the inclusion of platelet count in the ISTH criteria, which is excluded from the MHW criteria due to the frequent thrombocytopenia observed in patients with hematologic malignancies, particularly leukemia. Furthermore, the ISTH diagnostic criteria do not clearly define the cut-off values for FDP between moderate and marked elevations.

In 2017, the JSTH established new DIC diagnostic criteria (2017 version), which incorporate hypercoagulability markers such as soluble fibrin (SF) and thrombin-AT complex (TAT). According to a survey of 155 institutions treating pediatric leukemia cases in Japan, 72% used the former MHW DIC diagnostic criteria, whereas only 37% utilized the new JSTH DIC diagnostic criteria [21]. A multicenter

prospective study conducted between 2017 and 2021 validates the JSTH DIC diagnostic criteria [22]. In this study, DIC diagnosis rates were compared between the JSTH and ISTH criteria in 222 patients with coagulopathy (82 with hematologic malignancies, 86 with infections, and 54 with other conditions). Accordingly, the novel results showed a higher DIC diagnostic rate when using the JSTH criteria than when using the ISTH criteria [22].

Question 3 (CQ): Should antifibrinolytic agents be administered for DIC associated with acute promyelocytic leukemia during ATRA therapy?

Recommendation

We do not recommend the administration of antifibrinolytic agents to patients with DIC associated with APL during treatment with ATRA (strong recommendation/low certainty of evidence: GRADE 1C).

1. Background

Hematologic malignancies, especially APL, frequently develop into fibrinolysis-type DIC. Bleeding-related deaths occur in 5–10% of patients with APL within 28 days of chemotherapy initiation. Conversely, thrombosis develops in approximately 9% of the cases because of the coexistence of severe hypercoagulation in patients with DIC associated with APL. Antifibrinolytic agents, such as TA, may be used to control bleeding. However, the benefits of this approach remain unknown.

2. Recommendation rationale

- Balance between benefits and harms

In the systemic review, one randomized trial and two observational studies were included. A randomized trial [23] evaluating the benefit of TA during induction therapy for APL showed significant suppression of bleeding symptoms in the TA group. However, this trial was conducted before ATRA was introduced in clinical practice.

An observational study in Italy involving 268 patients with APL [24] showed no difference in the rate of premature death due to bleeding between patients with and without antifibrinolytic treatment. However, regarding the development of thrombosis, an observational study of 31 patients with APL [25] showed that four patients received ATRA and TA, and three of them developed thrombosis and subsequently died. The remaining patient died due to hemorrhage. From the above results, it should be noted that combination therapy with ATRA and TA, without the use of chemotherapeutic drugs, can lead to fatal thrombosis. Therefore, the harm outweighs the benefits.

- Certainty of the evidence

For the outcomes of bleeding-related death and thrombosis development, we judged the certainty of the evidence from observational studies to be low. We judged the overall certainty of the evidence to be 'moderate.'

- Values and preferences

Patients' values and preferences have not been evaluated based on current evidence.

- Cost and resource use

Notably, no evidence-based assessment of costs and resources has been conducted.

- Other ancillary matters (admissibility and feasibility)

We did not include clinical trials that validated the efficacy of TA in preventing bleeding-related deaths during standard chemotherapy, including ATRA and cytotoxic agents. Evidence from observational studies suggests that a combination of ATRA and TA may cause fatal thrombosis; however, the concurrent use of these two drugs is not strongly recommended.

3. Discussion and decision by voting

First vote: strong recommendation not to use: 12/13 (92%); weak recommendation not to use: 1/13 (8%).

Question 4 (CQ): Should recombinant thrombomodulin be administered for DIC with hematologic malignancies?

Recommendation

We recommend the administration of recombinant thrombomodulin (rTM) to patients with DIC associated with hematologic malignancies (Weak recommendation/Moderate certainty evidence: GRADE 2B).

1. Background

rTM was launched in 2008 and is widely used in clinical practice in Japan [26, 27]. rTM has anticoagulant activity

through the activation of protein C (PC) and antifibrinolytic activity through the activation of thrombin-activatable fibrinolysis inhibitors (TAFI). This dual mechanism provides a potential therapeutic effect on all types of DIC, including fibrinolytic inhibitory, fibrinolytic equilibrium, and marked fibrinolytic types [27]. The primary anticoagulant effect of rTM is PC activation through complex formation with thrombin, which is considered to be less conducive to bleeding [27]. However, it is unclear whether rTM has a clinical effect on DIC associated with hematologic malignancies compared with other coagulants.

2. Recommendation rationale

- Balance between benefits and harms

This systematic review analyzed 1338 patients from 14 studies, including a prospective study (randomized controlled trial [RCT]) (one report) [26], a post-marketing study (five reports) [28–32], a prospective observational study (one report) [33], and a retrospective controlled study (seven reports) [4, 34–39] (Tables 2, 3, Fig. 2). Furthermore, in evaluating the outcomes of DIC-resolution rate, hemorrhagic complications, and overall survival (OS) (28-day OS), rTM treatment demonstrated superiority in DIC-resolution rate and hemorrhagic complications compared with the control group [40]. However, there was no difference in mortality rates [40]. Compared with the treatment of underlying diseases, rTM treatment improves DIC-resolution rates and reduces the incidence of hemorrhagic complications [40]. Based on these findings, rTM is expected to have beneficial effects on all outcomes.

- Certainty of the evidence

We judged the certainty of the evidence for the outcomes of all-cause mortality, hemorrhagic complications, and DIC-resolution to be "moderate" (Evidence Profile). Based on these findings, we judged the overall certainty of the evidence to be "moderate."

- Values and preferences

Patient values and preferences were not assessed based on available evidence.

- Cost and resource use

Evidence-based assessments of costs and resources have not yet been conducted.

- Other ancillary matters (admissibility and feasibility)

The increase in the workload of medical personnel associated with the administration of this drug was small and

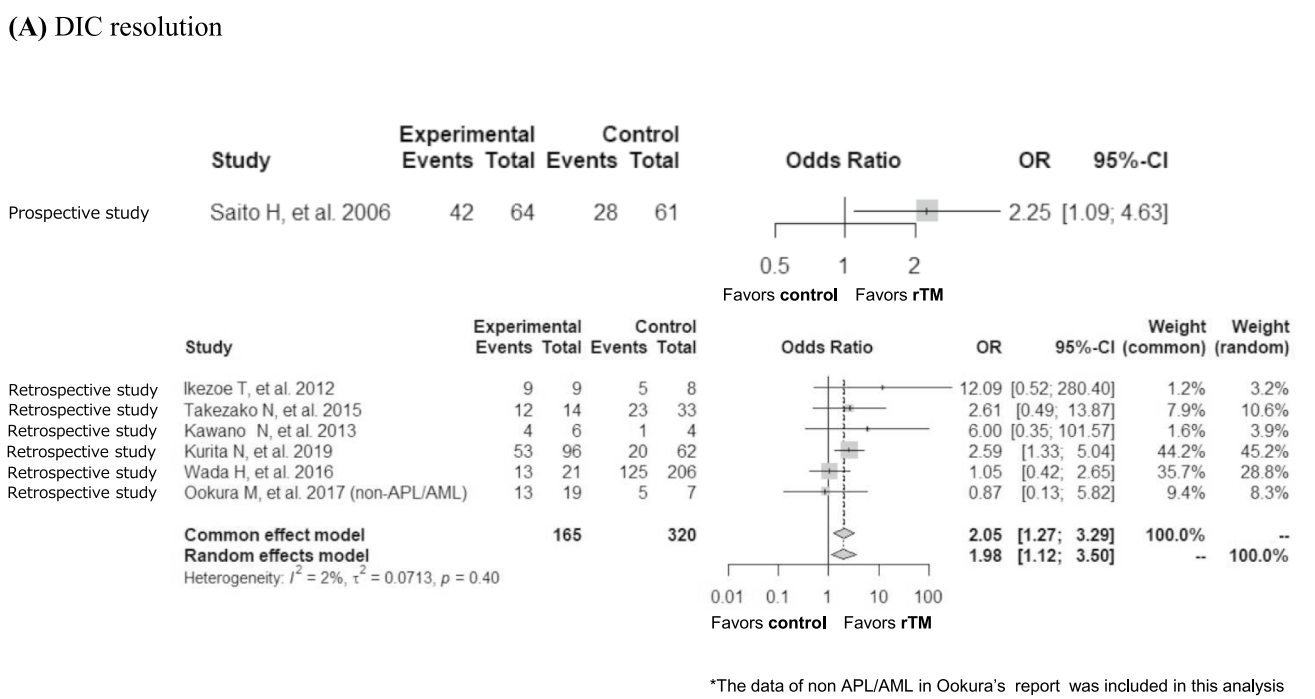

Fig. 2 Forest plot of the comparison: rTM vs. control**A** DIC resolution, **B** hemorrhagic complications, **C** overall survival

(B) Hemorrhagic complications

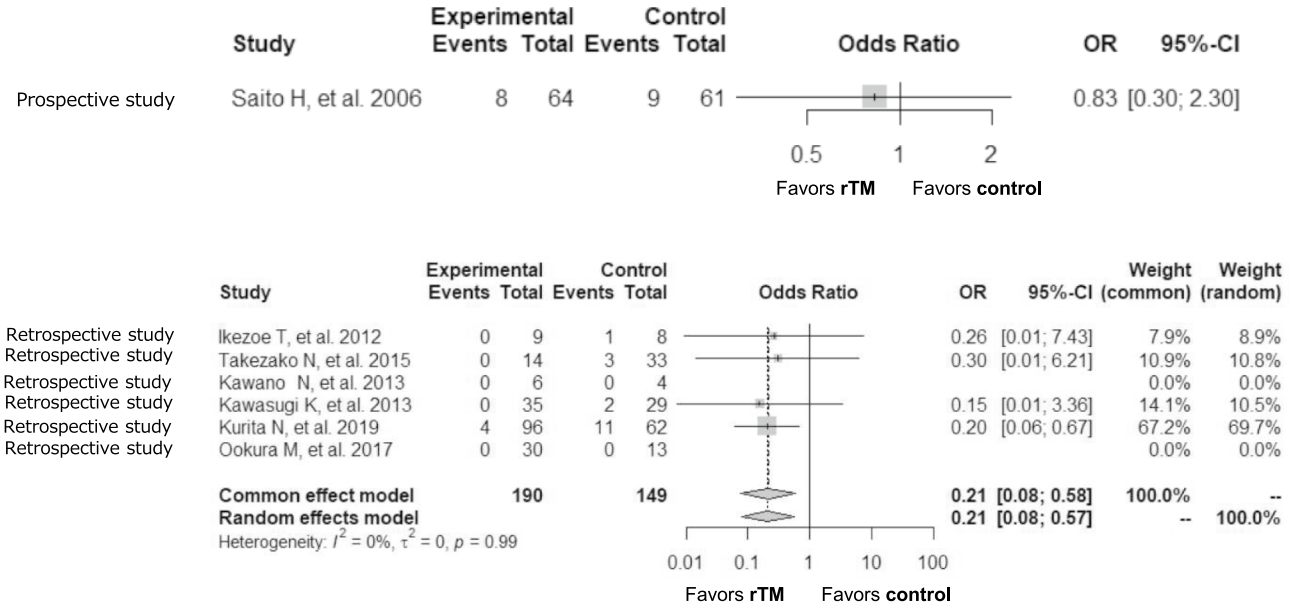

Fig. 2 (continued)

acceptable. It is widely used at many medical institutions in Japan.

3. Discussion and decision by voting

First vote: strong recommendation to use: 3/11 (27%); Weak recommendation to use: 8/11 (73%); two abstentions were observed due to COI.

Question 5 (CQ): Should heparin be administered for DIC associated with hematological malignancies?

Recommendation

We do not recommend the administration of unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), or danaparoid sodium (DS) to patients with DIC associated with hematological malignancies (Weak recommendation/ Low certainty of evidence: GRADE 2C).

1. Background

Heparins are classified as conventional UFH, relatively newer LMWH, and DS [2]. However, there is limited evidence regarding the efficacy of heparin treatment for DIC associated with hematologic malignancies [5], and it remains unclear whether heparin treatment provides any clinical benefits, such as DIC resolution or reduction in bleeding complications.

2. Recommendation rationale

- Balance between benefits and harms

The systemic review analyzed 341 patients from nine studies, including five RCTs and four retrospective controlled trials [4, 26, 34, 41–47]. The outcomes assessed were "DIC resolution rate," "hemorrhagic complications," and "overall survival (28-day OS)." The use of heparin demonstrated a 45–56.4% efficacy of the DIC-resolution rate as a beneficial outcome. However, heparin use is associated with a significant risk of bleeding exacerbation. Based on these findings, the balance between benefits and harms suggests that the potential adverse effects outweigh the benefits of heparin administration.

- Certainty of the evidence

Meta-analyses and qualitative assessments were not feasible; however, we determined the certainty of the evidence to be 'low' or 'very low' for all outcomes. Based on these findings, we concluded that the overall certainty of the evidence was "low."

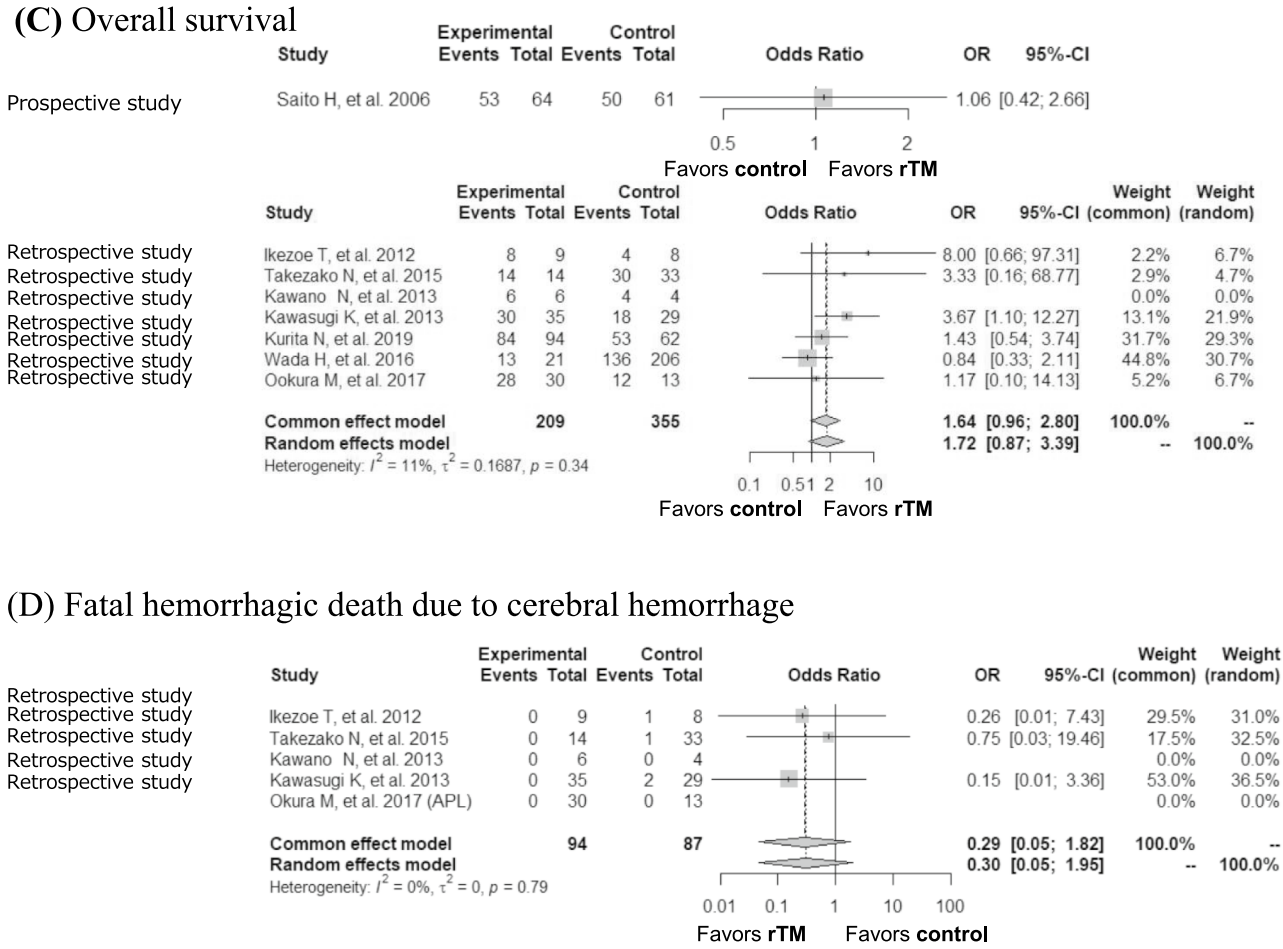

Fig. 2 (continued)

- Values and preferences

Patient values and preferences were not assessed based on the limited evidence.

- Cost and resource use

Evidence-based assessments of costs and resources were not performed.

- Other ancillary matters (admissibility and feasibility)

The additional workload for medical staff involved in administering this drug is minimal and manageable. Notably, it is administered in numerous medical institutions in Japan. However, if heparin administration is unavoidable, LMWH, which has a lower risk of hemorrhagic complications than UFH, should be considered.

3. Discussion and decision by voting

First vote: weak recommendation not to use: 11/13 (92%); strong recommendation not to use: 1/12 (8%).

Question 6 (CQ): Should serine protease inhibitors be administered for DIC associated with hematologic malignancies?

Recommendation

We do not recommend the administration of serine protease inhibitors (SPIs) to patients with DIC associated with hematologic malignancies (Weak recommendation/Low certainty of evidence: GRADE 2C).

The additional statement: SPI may be considered in cases of severe bleeding due to marked fibrinolytic DIC.

1. Background

Table 1 Summary of questions and recommendations

Question 1 (BQ)	What types of hematologic malignancies cases should DIC be suspected in?
Statement	Patients with acute leukemia, advanced-stage malignant lymphoma or hemophagocytic syndrome complicated by malignant lymphoma are more susceptible to DIC
Question 2 (BQ)	What are the appropriate DIC diagnostic criteria for patients with hematologic malignancies?
Statement	Diagnoses are made according to the DIC diagnostic criteria of the Japan Society for Thrombosis and Hemostasis (JSTH) (2017 version) or the DIC diagnostic criteria of the former Ministry of Health and Welfare (MHW) (1983 version)
Question 3 (CQ)	Should antifibrinolytic agents be administered for DIC associated with acute promyelocytic leukemia (APL) during ATRA therapy?
Recommendation	We do not recommend the administration of antifibrinolytic agents to patients with DIC associated with APL during treatment with ATRA (Strong recommendation/Low certainty of evidence: GRADE 1C)
Question 4 (CQ)	Should recombinant thrombomodulin (rTM) be administered for DIC associated with hematologic malignancies?
Recommendation	We recommend the administration of recombinant thrombomodulin (rTM) to patients with DIC associated with hematologic malignancies (Weak recommendation/Moderate certainty evidence: GRADE 2B)
Question 5 (CQ)	Should heparin be administered for DIC associated with hematologic malignancies?
Recommendation	We do not recommend the administration of unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), or danaparoid sodium (DS) to patients with DIC associated with hematological malignancies (Weak recommendation/Low certainty of evidence: GRADE 2C)
Question 6 (CQ)	Should serine protease inhibitors (SPIs) be administered for DIC associated with hematologic malignancies?
Recommendation	We do not recommend the administration of serine protease inhibitors (SPIs) to patients with DIC associated with hematologic malignancies (Weak recommendation/Low certainty of evidence: GRADE 2C) The additional statement: SPI may be considered in cases with severe bleeding due to marked fibrinolytic-type DIC
Question 7 (FRQ)	Should antithrombin (AT) be administered for DIC associated with hematologic malignancies?
Statement	The use of AT should be considered when the AT activity level is reduced to ≤ 70%
Question 8 (BQ)	How should we manage replacement therapy for DIC associated with hematologic malignancies?
Statement	Replacement therapy should be implemented based on clinical guidelines according to the recommended trigger and target levels of transfusion, including PC and FFP infusion For platelet transfusion, it is desirable to set the trigger value at ≤ 30,000/μL with a target of ≥ 50,000/μL (at least ≥ 30,000/μL) For fresh frozen plasma infusion, it is desirable to set the trigger value at ≤ 100–150 mg/dL and PT-INR ≥ 2.0, with a target of fibrinogen ≥ 150 mg/dL and PT-INR of ≤ 1.5
Question 9 (BQ)	Under what circumstances should worsening of DIC/coagulopathy be considered with regard to the treatment of hematologic malignancies?
Statement	The high-risk group of patients with tumor lysis syndrome (Burkitt's lymphoma and acute leukemia with leukocytosis) should be aware of the exacerbation of DIC/coagulation abnormalities after the initiation of chemotherapy. In contrast, low-risk groups with multiple myeloma (MM) and chronic lymphocytic leukemia (CLL) rarely develop tumor lysis syndrome; however, the risk of coagulopathy is also increasing with the advent of new molecularly targeted drugs During chimeric antigen receptor (CAR)-T therapy, cytokine release syndrome and associated DIC develop owing to macrophage activation. Therefore, appropriate response and management of these issues are critical for successful treatment

SPIs, including nafamostat mesylate and gabexate mesylate, are active in the absence of AT and can, therefore, be effective even in patients with DIC with reduced AT activity [2]. In addition, SPIs are characterized by fewer hemorrhagic complications than heparin. Consequently, they can be used to treat DIC associated with APL, which has a pronounced bleeding tendency [2]. However, given that SPI is currently only available in Japan and its use is declining [5], its clinical efficacy, such as DIC resolution or reduction of hemorrhagic complications, remains unclear.

2. Recommendation rationale

- Balance between benefits and harms

The systemic review analyzed one RCT and five retrospective controlled trials [35, 38, 39, 45, 48, 49]. Examination of the DIC-resolution rate, hemorrhagic complications, and overall survival (28-day OS) revealed that the clinical efficacy of SPIs is extremely limited. However, the incidence of hemorrhagic complications tended to be lower in the SPIs cohort than in the heparin cohort. SPI requires continuous infusion for 24 h due to their short half-life [2], and intravenous drip leakage may cause skin ulceration and necrosis [2]. Therefore, at high concentrations, it damages endothelial cells of blood vessels [2]. Hyperkalemia and hyponatremia may occur in patients with impaired renal function [2]. Based on the above findings, the adverse effects of SPI outweigh its benefits.

Table 2 Studies evaluating rTM for DIC associated with hematologic malignancy based on SR and Meta-analysis (Question 4)

Reference	Study design	P	I	C	O	rTM group	Control group
Saito et al. (2006)	Prospective cohort	125 patients (AML = 71, ALL = 23, APL = 4, CML = 6, ML = 14, ATL = 1, MDS = 4, Others = 2) with DIC	rTM ($n = 64$)	Unfractionated heparin ($n = 61$)	DIC resolution, OS, hemorrhagic complications	DIC resolution: 65%, OS: 82%, hemorrhagic complications: 12%	DIC resolution: 45%, OS: 81%, hemorrhagic complications: 14%
Ikezoe et al. (2012)	Retrospective cohort	17 APL patients with DIC	rTM ($n = 9$)	LMWH ($n = 8$)	DIC resolution, OS, hemorrhagic complications	DIC resolution: 100%, OS: 88%, hemorrhagic complications: 0%	DIC resolution: 62%, OS: 50%, hemorrhagic complications: 12%
Takezako et al. (2012)	Retrospective cohort	47 AML patients with DIC	rTM ($n = 14$)	LMWH ($n = 33$)	DIC resolution, OS, hemorrhagic complications	DIC resolution: 85%, OS: 100%, hemorrhagic complications: 0%	DIC resolution: 69%, OS: 90%, hemorrhagic complications: 9%
Kawano et al. (2013)	Retrospective cohort	10 APL patients with DIC	rTM ($n = 6$)	SPI ($n = 4$)	DIC resolution, OS, hemorrhagic complications	DIC resolution: 66%, OS: 100%, hemorrhagic complications: 0%	DIC resolution: 25%, OS: 100%, hemorrhagic complications: 0%
Kurita et al. (2019)	Retrospective cohort	158 patients (AML = 59, APL = 35, ALL = 27, ML = 29, MM = 1, MDS = 1, Others = 6) with DIC	rTM ($n = 96$)	LMWH, gabexate mesilate ($n = 62$)	DIC resolution, OS, hemorrhagic complications	DIC resolution: 55%, OS: 89%, hemorrhagic complications: 17%	DIC resolution: 32%, OS: 85%, hemorrhagic complications: 17%
Wada et al. (2016)	Retrospective cohort	227 patients (Data not shown about the underlying disease) with DIC	rTM ($n = 21$)	Gabexate mesilate ($n = 206$)	DIC resolution, OS, hemorrhagic complications	DIC resolution: 61%, OS: 61%, hemorrhagic complications: not available	DIC resolution: 60%, OS: 66%, hemorrhagic complications: not available
Okura et al. (2017)	Retrospective cohort	17 APL and 26 AML patients with DIC	rTM ($n = 30$)	Gabexate mesilate ($n = 13$)	DIC resolution, OS, hemorrhagic complications	DIC resolution: 68%, OS: 93%, hemorrhagic complications: 0%	DIC resolution: 71%, OS: 92%, hemorrhagic complications: 0%
Kawasugi et al. (2013)	Retrospective cohort	64 APL patients with DIC	rTM ($n = 35$)	LMWH, SPI ($n = 29$)	DIC resolution, OS, hemorrhagic complications	DIC resolution: not available, OS: 85%, hemorrhagic complications: 0%	DIC resolution: not available, OS: 62%, hemorrhagic complications: 6%

DIC was diagnosed using the JMHW criteria in all studies except for one by Ikezoe et al., in which the JMHW and ISTH criteria were used. DIC, disseminated intravascular coagulation; JMHW, Japanese Ministry of Health and Welfare; ISTH, International Society on Thrombosis and Hemostasis; OS, overall survival; rTM, recombinant thrombomodulin; LMWH, low-molecular-weight heparin; SPI, serine protease inhibitor; GM, gabexate mesylate; AML, acute myeloid leukemia; APL, acute promyelocytic leukemia; CML, chronic myeloid leukemia; ML, malignant lymphoma; ATL, adult T-cell leukemia/lymphoma; MDS, myelodysplastic syndrome; MM, multiple myeloma. Treatment outcomes were evaluated based on the survival rate 28 days after treatment, except for the report by Kurita report (30 days)

Table 3 GRADE evidence profile: rTM administration for DIC associated with hematologic malignancy (Question 4)

Certainty assessment							Number of patients		Effect	Certainty	Importance
Number of Studies	Study design	Risk of bias	Inconsistencies	Indirectness	Imprecision	Other considerations	rTM	Control	Relative (95% CI)		
Overall survival											
1	RCT	Not serious	Not serious	Not serious	Serious	None	53/64 82.80%	50/61 81.90%	RR 1.06 (0.42–2.66)	⨁⨁⨁◯ Middle	Important
7	Retrospective Study	Serious	Not serious	Not serious	Serious	None	183/209 87.60%	277/355 72.40%	OR 1.72 (0.87–3.39)	⨁⨁◯◯ Low	Important
Hemorrhagic complications											
1	RCT	Not serious	Not serious	Not serious	Serious	None	8/64 12.50%	9/61 14.70%	RR 0.83 (0.30–2.3)	⨁⨁⨁◯ middle	Important
6	Retrospective Study	serious	Not serious	Not serious	Not serious	None	4/190 2.10%	17/149 11.40%	OR 0.21 (0.08–0.57)	⨁⨁◯◯ Low	Important
DIC resolution											
1	RCT	Not serious	Not serious	Not serious	Not serious	None	42/64 65.60%	28/61 45.90%	RR 2.25 (1.09–4.63)	⨁⨁⨁◯ middle	Important
6	Retrospective Study	serious	Not serious	Not serious	Not serious	None	104/165 63.00%	179/320 55.90%	OR 1.98 (1.12–3.50)	⨁⨁◯◯ Low	Important

GRADE, Grading of Evidence, Assessment, Development and Evaluation; CI, confidence interval; RR, risk ratio

- Certainty of the evidence

We judged the certainty of the evidence for all-cause mortality, hemorrhagic complications and DIC withdrawal outcomes to be 'low' or 'very low.' Based on these findings, we concluded the overall certainty of the evidence was "low."

- Values and preferences

Patients' values and preferences have not been assessed based on limited evidence.

- Cost and resource use

Evidence-based assessments of costs and resources have not yet been made.

- Other ancillary matters (admissibility and feasibility)

The additional workload for the medical personnel involved in administering this drug is minimal and manageable. It can also be administered at many medical institutions in Japan. There is no accumulation of high-quality evidence, including RCTs, and the evidence is limited. However, in cases of marked fibrinolytic-type DIC, SPIs may be considered for severe bleeding [9, 10].

3. Discussion and decision by voting

First vote: weak recommendation to use 1/12 (8%), weak recommendation not to use 8/12 (67%), and strong recommendation not to use 3/12 (25%).

Second vote: weak recommendation not to use: 10/12 (83%); strong recommendation not to use: 2/10 (17%).

*Based on the discussion, we decided to add another statement, "SPI may be considered in cases with severe bleeding due to marked fibrinolytic-type DIC."

Question 7 (FRQ): Should antithrombin be administered for DIC associated with hematologic malignancies?

Statement

The use of AT should be considered when the AT activity level is reduced to ≤ 70%.

Rationale

AT is a physiologic protease inhibitor that inhibits the activity of coagulation factors, including thrombin and factor Xa [2]. Therefore, decreased AT levels reflect several medical conditions, including hypercoagulability, and are included in the JSTH DIC diagnostic criteria (2017 version) [52]. DIC associated with hematologic malignancies is less likely to cause a significant reduction in AT levels (≤ 70%); however, markedly decreased AT levels (≤ 50%) have been identified as a poor prognostic factor [15, 53]. In Japan, AT has been used in approximately 10–20% of anticoagulant therapies for DIC associated with hematologic malignancies [5, 37]. However, the clinical efficacy and potential adverse effects of AT in DIC associated with hematological malignancies remain unclear.

A systematic review analyzed two prospective observational studies ($n = 34$, hematologic malignancy) evaluating the efficacy of AT in patients with DIC associated with hematologic malignancies [54, 55]. In both studies, there was insufficient evidence to determine the benefits and disadvantages regarding the DIC-resolution rate, hemorrhagic complications, and overall survival (28-day OS). Consequently, the evidence must be considered limited.

In 2016, recombinant AT (rAT) was introduced into clinical practice. A post-marketing study (interim report) on rAT showed a gradual accumulation of cases, demonstrating its efficacy and safety [56]. A critical advantage of rAT is its ability to avoid the infection risks associated with human plasma and weight-based dosing (36–72 IU/kg/day). Further studies are needed to verify the clinical efficacy and safety of rAT in patients with DIC associated with hematological malignancies. Based on current clinical practice in Japan and the available observational studies, we recommend that "administering AT to patients with DIC associated with hematologic malignancies may be considered if AT activity is reduced to ≤ 70%."

Question 8 (BQ): How should we manage replacement therapy for DIC associated with hematologic malignancies?

Statement

Replacement therapy should be implemented based on clinical guidelines according to the recommended trigger and target levels of transfusion, including PC and FFP infusion.

For platelet transfusion, it is desirable to set the trigger value at ≤ 30,000/μL with a target of ≥ 50,000/μL (at least ≥ 30,000/μL).

For fresh frozen plasma infusion, it is desirable to set the trigger value at ≤ 100–150 mg/dL and PT-INR ≥ 2.0, with a target of fibrinogen ≥ 150 mg/dL and PT-INR of ≤ 1.5.

Rationale

In DIC treatment, treatment of the underlying disease is essential, and transfusion of PC and/or FFP should be performed if necessary [2]. Generally, clinical practice guidelines recommend that replacement therapy be determined based on bleeding symptoms rather than laboratory abnormalities. However, there are currently no specific evidence-based guidelines for DIC replacement therapy in Japan or other countries. Instead, these treatments are performed empirically according to domestic and international guidelines, including the PC/FFP guidelines of the Japan Society of Transfusion Medicine and Cell Therapy (JSTMCT) (2019 version), the European Leukemia Net (ELN) Guidelines (2019 version), and other clinical practice guidelines [2, 57–61] (Table 4). These guidelines outline the triggers and target values for blood transfusion therapy based on clinical conditions.

In Japan, the JSTMCT guidelines (2019 version) set the platelet transfusion trigger in patients who receive chemotherapy and/or hematopoietic stem cell transplantation for hematologic malignancies (excluding APL) at 10,000/μL [2]. However, for DIC associated with APL, due to a higher risk of bleeding, expert consensus suggests a platelet transfusion trigger of 20,000–50,000/μL, with a recommended trigger of ≤ 30,000/μL [57]. In contrast, the JSTMCT guidelines for FFP transfusion (2019 version) do not specifically address DIC in nonsurgical cases, largely because of the lack of RCTs on FFP replacement therapy in patients with DIC [58]. However, expert consensus suggests that FFP infusion is medically feasible with a high probability since patients with DIC often exhibit rapid consumption of coagulation, anticoagulation, and antifibrinolytic factors [58]. Notably, no specific triggers are indicated in the FFP guidelines; however, the blood transfusion therapy guidelines (Ministry of Health, Labor and Welfare, 2005 version) suggest PT-INR ≥ 2.0 or PT ≤ 30% as reference values, based on the "30% rule" that 30% of normal coagulation factor activity is required for hemostasis [58, 61].

Clinical practice guidelines for hematologic malignancy (Japanese Society of Hematology, 2023 edition) highlight that in patients with DIC, low fibrinogen levels (< 100 mg/dL), elevated white blood cell counts (> 20,000/μL), and low platelet counts (< 30,000/μL) are critical risk factors for severe bleeding, as shown in a retrospective analysis of the JALSG APL trial [60, 62, 63].

Therefore, based on these significant risk factors, prophylactic platelet transfusion is recommended to maintain a platelet count of at least 50,000/μL or, at the very least, 30,000/μL. In addition, FFP transfusion is recommended to maintain fibrinogen levels of ≥ 150 mg/dL.

In European countries, the ELN guidelines (2019 version) also provide recommendations regarding transfusion trigger values, which include fibrinogen ≤ 100–150 mg/dL, platelet count ≤ 30,000–50,000/μL, and PT-INR ≥ 1.5. Laboratory tests for platelets and coagulation markers, including PT, activated partial thromboplastin time, fibrinogen, and fibrinogen degradation products, should be conducted at least once daily until the clinical findings have resolved [59].

Based on the Japanese and international DIC guidelines [2, 57–61] (Table 4), we propose the following trigger and target values for replacement therapy: frequent monitoring and appropriate blood-transfusion therapy should be conducted based on clinical pathology, established guidelines, and target values. Flexibility in response to a patient's condition and the medical environment is also crucial [1–6].

Table 4 Summary of the trigger values and target values of blood transfusions in each guideline (Question 8)

	Platelet		Fibrinogen		PT-INR	
	Trigger (μL)	Target Value (μL)	Trigger (mg/dL)	Target value (mg/dL)	Trigger	Target Value
Japanese Society of Thrombosis and Hemostasis (Expert Consensus) (2009)	20,000–50,000	Not described	100	Not described	≥ 2.0 or PT ≤ 30%	Not described
Japan Society for Transfusion Medicine and Cell Therapy (2019)	30,000	Not described	Not described	Not described	≥ 2.0 or PT ≤ 30%	Not described
Japanese Society of Hematology (2023)	Not described	50,000 or greater (at least 30,000 or greater)	Not described	150or greater	Not described	Not described
ELN guideline (2019)	30,000–50,000	Not described	100–150	Not described	≥ 1.5	Not described
Japanese Society of on Thrombosis and Hemostasis (DIC guideline) (2024)	30,000	50,000 or greater (at least 30,000 or greater)	100–150	> 150	≥ 2.0	≤ 1.5

Question 9 (BQ): Under what circumstances should worsening of DIC/coagulopathy be considered with regard to the treatment of hematologic malignancies?

Statement

The high-risk group of patients with tumor lysis syndrome (TLS) (Burkitt's lymphoma and acute leukemia with leukocytosis) should be aware of the exacerbation of DIC/coagulation abnormalities after the initiation of chemotherapy. In contrast, low-risk groups with MM and chronic lymphocytic leukemia (CLL) rarely develop tumor lysis syndrome (TLS); however, the risk of coagulopathy is also increasing with the advent of new molecularly targeted drugs.

During chimeric antigen receptor (CAR)-T therapy, cytokine release syndrome and associated DIC develop owing to macrophage activation. Therefore, appropriate response and management of these issues are critical for successful treatment.

Rationale

Among hematologic malignancies, Burkitt's lymphoma and acute leukemia with marked leukocytosis are associated with a high risk for TLS, an oncologic emergency caused by the massive lysis of tumor cells [64]. This process releases intracellular substances, particularly purines and electrolytes (potassium and phosphorus), leading to TLS [64]. Clinically, TLS presents with symptoms such as nausea, vomiting, lethargy, and arrhythmia. Laboratory tests typically show elevated levels of uric acid, potassium, and phosphate, and decreased calcium levels. Therefore, appropriate risk classification and treatment for TLS are essential [64]. In addition, TLS has been associated with the exacerbation of DIC [65]. Nuclear proteins, such as high-mobility group box 1 (HMGB1) and histone H3, released during tumor cell decay may contribute to the development of DIC [66]. The standard evaluation and treatment of DIC/coagulopathy after TLS remain unclear. Therefore, patients should be assessed using established DIC diagnostic criteria, and anticoagulation therapy should be selected based on clinical conditions. However, optimal therapeutic agents remain unclear. Among anticoagulant therapies, rTM has also been demonstrated to adsorb HMGB1 and histone H3, suggesting its potential for managing DIC associated with TLS [27]. The advent of new molecularly targeted therapies, such as anti-CD38 antibody drugs and Venetoclax, has raised concerns regarding the development of TLS in patients with MM and CLL, which were previously considered low risk for TLS [67, 68]. This concern is supported by the increasing number of TLS cases reported in the Pharmaceuticals and Medical Devices Agency Adverse Drug Reaction database [69].

CAR-T cell therapy has shown remarkable clinical efficacy in patients with relapsed/refractory malignant lymphoma, acute lymphoblastic leukemia, and MM. However, cytokine release syndrome (CRS), which is characterized by high fever, hypotension, and central nervous system (CNS) dysfunction, is common with CAR-T therapy [70]. Furthermore, in some cases, CRS is complicated by DIC. Therefore, appropriate management of CRS is critical to the success of CAR-T therapy.

In a study of 100 patients receiving CAR-T cell therapy in China, approximately 50% developed coagulation disorders, including elevated FDP and decreased fibrinogen, within 6–20 days after CAR-T cell therapy. Seven patients were diagnosed with DIC based on ISTH diagnostic criteria [71]. Another study conducted in China, analyzing 53 patients undergoing CAR-T cell therapy, found that approximately 50% exhibited coagulation abnormalities, the severity of which correlated with the CRS grade [72]. In addition, a Japanese study of 25 patients with diffuse large B-cell lymphoma undergoing CAR-T cell therapy showed fibrinolytic suppression and relative hypercoagulability characterized by elevated plasminogen activator inhibitor-1 (PAI-1) levels and increased fibrin production during the early phase of CRS [73]. Subsequently, there was an improvement in PAI-1 and various coagulation test values on day 13, which coincided with an improvement in CRS [73]. Therefore, macrophage activation associated with cytokine storms may be involved in the development of DIC after CAR-T therapy.

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Declarations

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