Supplementary Methods

1. Inclusion criteria
Patients with disseminated intravascular coagulation (DIC) associated with hematological malignancy or infection were recruited. DIC was diagnosed according to the diagnostic criteria established by the Japanese Ministry of Health and Welfare (JMHW DIC criteria) [1]. Inclusion criteria were as follows: i) when a DIC score of more than 7 points, or more than 4 points in the presence of severe thrombocytopenia because of the presence of bone marrow failure, DIC is diagnosed. When a DIC score of 6 points or 3 points in the presence of severe thrombocytopenia because of the presence of bone marrow failure, two or more positive findings from supplementary tests are needed to reach a diagnosis of DIC; ii) negative thrombomodulin alfa (TM-α) skin test; iii) ≥ 15 years old; iv) bodyweight ≤ 100 kg; and v) inpatient status [2].

2. Exclusion criteria
Exclusion criteria were as follows: fatal or life-threatening bleeding (intracranial, gastrointestinal or pulmonary bleeding); high probability of developing fatal or life-threatening bleeding; history (within 1 year) of cerebrovascular disorder (cerebral bleeding, cerebral infarction); recent central nervous system surgery or trauma; history of hypersensitivity to protein preparations or unfractionated heparin; pregnancy, nursing or potential pregnancy; positive TM-α skin test; dialysis therapy or severely impaired drug excretion because of kidney disorder; fulminant hepatitis, decompensated liver cirrhosis, or other serious liver disorder; expected difficulty in ensuring adequate study drug infusion, or obtaining efficacy and safety data; administration of another study drug within 6 months prior to the current study; participation in previous clinical studies on TM-α; administration of unfractionated heparin within 3 months prior to start of study drug infusion; or patient judged as inappropriate at the discretion of investigators [2].

3. Method of administration of study drugs and blood collection
With the double-dummy method, patients in the TM-α group received TM-α and heparin placebo, and patients in the heparin group received heparin sodium and TM-α placebo. TM-α was administered for 6 consecutive days, as 0.06 mg/kg drip-infused for 30 min once daily. Heparin sodium was administered for 6 consecutive days at 8 units per kilogram of bodyweight per hour drip-infused 24 h/day.
Measurement of hemostatic parameters was conducted on the day of registration, at baseline and at the end of study drug infusion (or withdrawal) to measure the following: fibrin and fibrinogen degradation products (FDP); fibrinogen; prothrombin time (PT) ratio; activated partial thromboplastin time (APTT); platelet count; antithrombin; thrombin-antithrombin
complex (TAT); plasmin-plasmin inhibitor complex (PIC); D-dimer; α2 plasmin inhibitor (α2-PI); protein C (PC); plasminogen activator inhibitor-1 (PAI-1); and fibrin monomer complex (FMC).

![Table]

| Item                        | Timing                      | Day of registration 1) | Day of start of admin. | Day 2 of admin. | Day 3 of admin. | Day 4 of admin. | Day 5 of admin. | Day 6 of admin. | Day of completion of admin. 2) |
|-----------------------------|----------------------------|-------------------------|------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------------------|
| Administration of study drug| TM-α                        |                         | Before admin.          | Before admin.   | Before admin.   | Before admin.   | Before admin.   | Before admin.   | After completion of admin. of heparin |
| Heparin sodium              |                             |                         | Before admin.          |                 |                 |                 |                 |                 |                             |
| Hemostatic parameters       | Items of institutional measurement (FDP, fibrinogen, platelet count, PT ratio, and APTT) | ● | ○ | ○ | ○ | ○ | ○ | ○ | ●  |
|                            | Items of intensive measurement (TAT, PIC, D-dimer, α2-PI, PC, PAI-1, FMC, and antithrombin) | ● | ●* | ○ | ○ | ○ | ○ | ○ | ●  |

●: Performed without fail. ○: Performed at investigator’s discretion.

1) Examinations for the day of registration could be performed on the day before registration. When examinations on the day of registration were performed within 24 h before administration of the study drug, the results could be used as examination data before administration of the drug on the day of start of administration.

2) When administration of the study drug was discontinued before study completion, measurement of hemostatic parameters could be performed in the range of one day before to one day after the day of indispensable examinations after the completion of drug administration. This condition, however, was applied only when such examinations could not be performed for special reasons.

*: Within 24 h before administration of the study drug.
4. Definitions of the leukemia and non-leukemia groups

For analysis of changes in platelet count or JMHW DIC score, patients were classified into two groups based on JMHW DIC criteria (leukemia or non-leukemia group) [1]. When the number of megakaryocytes markedly decreases due to hematological malignancy, aplastic anemia, or antitumor agent administration, the number of platelets markedly decreases irrespective of the underlying diseases or their severity. These patients were grouped for convenience as the leukemia group without regard to morbidities and other patients were grouped as the non-leukemia group.

4-1. Classification into two groups (leukemia or non-leukemia) when the direct cause of DIC is hematological malignancy

The direct cause for the onset of DIC should be among the hematological malignancies listed below.

1) Acute myeloid leukemia; 2) acute lymphocytic leukemia; 3) chronic myeloid leukemia; 4) chronic lymphocytic leukemia; 5) adult T-cell leukemia; 6) myelodysplastic syndrome; 7) malignant lymphoma; 8) multiple myeloma; or 9) others.

(i) Patients with underlying diseases falling under items 1–6 above (leukemia and myelodysplastic syndrome) were classified to the leukemia group.

(ii) Patients with underlying diseases falling under items 7–9 above (malignant lymphoma, multiple myeloma and others) were classified to the two groups (leukemia or non-leukemia) according to predefined procedures in the protocol. The classification was made in consideration of the cause of decrease in platelet count (consumption of platelets or underlying diseases).

4-2. Classification into two groups (leukemia or non-leukemia) when direct cause of DIC is infection

(i) When there were no treatments or complications accompanying a decrease in platelet count (administration of anticancer agents, hematological malignancy, or aplastic anemia), patients were classified to the non-leukemia group.

(ii) When there were treatments or complications accompanying a decrease in platelet count (administration of anticancer agents, hematological malignancy, or aplastic anemia), patients were classified to the two groups (leukemia or non-leukemia) according to predefined procedures in the protocol. The classification was made in consideration of the causes of the decrease in platelet count.
References

1. Kobayashi N, Maekawa T, Takada M, Tanaka H, Gonmori H. Criteria for diagnosis of DIC based on the analysis of clinical and laboratory findings in 345 DIC patients collected by the Research Committee on DIC in Japan. *Bibliotheca Haematologica*. 1983:265-75.

2. Saito H, Maruyama I, Shimazaki S, Yamamoto Y, Aikawa N, Ohno R, et al. Efficacy and safety of recombinant human soluble thrombomodulin (ART-123) in disseminated intravascular coagulation: results of a phase III, randomized, double-blind clinical trial. *J Thromb Haemost*. 2007;5:31-41.