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Short communication

Effects of recombinant thrombomodulin on long-term prognosis after allogeneic hematopoietic stem cell transplantation

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ABSTRACT

We investigated the effects of early recombinant thrombomodulin (rTM) treatment on long-term prognosis after hematopoietic stem cell transplantation (HSCT). Subjects included 300 patients who underwent allogeneic HSCT (131 in the rTM(+) group and 169 in the rTM(−) group). The control group received heparin or no anti-coagulation therapy. When we examined patients with confirmed complications (day 1–100), the frequencies of acute graft-versus-host disease (aGVHD) and thrombotic microangiopathy (TMA) were significantly lower in the rTM(+) group, while the frequencies of veno-occlusive disease did not show such differences. rTM administration was associated with significant differences in the cumulative incidence of aGVHD (any grade and II-IV grades) and TMA. The cumulative overall survival probability was significantly higher in the rTM(+) group (42.3% versus 26.2%, $p = .037$). Therefore, some causes of a poor prognosis included aGVHD and TMA. The present findings suggest that rTM plays a preventive role in transplant-related complications, such as aGVHD and TMA, after allogeneic HSCT.

In a healthy blood system, there are important factors that break the amplifying reaction of excessive coagulation and prevent morbid thrombosis [1]. Some of them are produced by endothelial cells, such as thrombomodulin (TM) [2]. TM has five structural domains including a lectin-like domain, EGF-like domain, O-type carbohydrate chain-binding domain, cell membrane penetration domain, and cytoplasmic domain [3]. In addition to an anticoagulant effect, TM has anti-inflammatory actions. Recently, the mechanism of the anti-inflammatory action has been clarified. It depends on inactivation of danger-associated molecular patterns and neutralization of complement proteins. Recombinant TM (rTM) is structured so that it recognizes a domain of TM on cells in the blood vessel endothelium in vivo. Similar to normal membrane-type TM, rTM acts by binding to thrombin to inhibit coagulation [4]. As a result, the thrombin–rTM complex activates protein C-inactivating factor VIIIa and Va in the presence of protein S [5,6]. In addition, rTM binds to high mobility group box 1 (HMGB1) and disrupts its cytotoxic function [6].

Hematopoietic stem cell transplantation (HSCT) can achieve complete remission of blood cancer. However, HSCT causes serious transplant-related complications. Representative complications are graft-versus-host disease (GVHD), veno-occlusive disease (VOD), and thrombotic microangiopathy (TMA) [7,8]. The pathophysiology of acute GVHD (aGVHD) is very complicated. One of its causes is the components of conditioning regimens and the activation of lymphocyte in conjunction with immunity and inflammation as well as the sequential cytokine production. Some T cells derived from donors play major role in aGVHD [9]. A patient who receives HSCT experiences a vascular disorder, but it is the endothelial disorder to become base [10,11]. When endothelial cells are stimulated continually by cytotoxic T cells, a patient is recognized as having GVHD [12]. In addition, HMGB1 is closely associated with HSCT-related complications, because it is mobilized from apoptotic or necrotic cells by the conditioning treatment for HSCT [13]. Therefore, rTM might be useful for transplantation-associated coagulopathy (TAC) after HSCT. Indeed, there are some reports on the efficacy of rTM therapies for TAC, including VOD and TMA [14–17]. In the present study, we investigated the effects of early rTM treatment on the long-term prognosis of patients in our previous studies [13,18,19].

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The subjects in this study were 300 Japanese patients who underwent allogeneic HSCT at several institutions in Japan. Patient diagnoses at transplantation were 108 cases of acute myeloblastic leukemia, 65 cases of acute lymphoblastic leukemia, 50 cases of myelodysplastic syndrome, and 77 cases of other disorders. The donor sources were 155 bone marrow transplantations, 64 peripheral blood stem cell transplantations, and 81 cord blood transplantations. Written informed consent was obtained from all patients, who were registered by faxing documents to the Kansai Medical University prior to HSCT. Although the data of these patients were published previously [13,17–19]. The 172 male and 128 female allogeneic HSCT patients ranged in age from 21 to 76 years (median: 45 years). The conditioning regimen was total body irradiation for 211 patients and non-total body irradiation for 89. The rTM, consisting of daily doses of 380 units/kg (Asahi Kasei Pharma, Tokyo, Japan), was administered as a preventive therapy for TAC. This protocol was completed during days 4 to 14 after HSCT. An anticoagulation regimen of 5000 U heparin, 24 h per day, was used prior to rTM administration. Control groups were administered further heparin instead of the rTM. In addition, patients who received no anticoagulant were also included in the control groups. The following complications were reported after HSCT. The presence of aGVHD, VOD, and TMA as determined by the chief physician in each facility with reference to previous reports concerning aGVHD [20,21], VOD [22], and TMA [23]. Overall survival (OS) was defined as the time from initial diagnosis to the time of death from any cause or the date when the patient was last known to be alive. Univariate analyses of OS were performed using the Kaplan-Meier product-limit method with the log-rank test and Cox proportional hazards model. Cumulative incidence (CI) of competing events analysis was performed using the EZR software.

When we examined patients with confirmed complications (day 1–100), the frequencies of aGVHD and TMA were significantly lower in the rTM(+) group compared with that of VOD (Table 1). rTM administration was associated with significant differences in the CI of aGVHD (any grade and II-IV grades) and TMA (Table 1). Furthermore, mortalities were significantly lower in the rTM(+) group at day 100 (Table 1). The cumulative OS probability was significantly higher in the rTM(+) group (42.3% versus 26.2%, $p = .037$) (Fig. 1).

Allogeneic HSCT was established as a therapeutic strategy for hematological disorders, but aGVHD remains as a problem of this treatment [24]. Many organs are affected by GVHD, but the most affected organs are the skin, gastrointestinal tract, and liver [24]. The T-cells of the donor recognize alloantigens of the host. Another characteristic that effector T cells differentiate [25]. As a result, these cells cause inflammation at the local site, which progresses to tissue damage [25]. Therefore, the existence of activated T cells is regarded as indispensable for the onset of aGVHD [26]. Damage to endothelial cells is regarded as a common feature of vascular complications in patients undergoing allogeneic HSCT [27]. In the present study, we found that the frequencies of aGVHD and TMA were significantly lower in the rTM(+) group, and rTM administration was associated with significant differences in the CI of aGVHD (all grade and II-IV grades) and TMA. These findings suggest that rTM can lessen the endothelial dysfunction after HSCT.

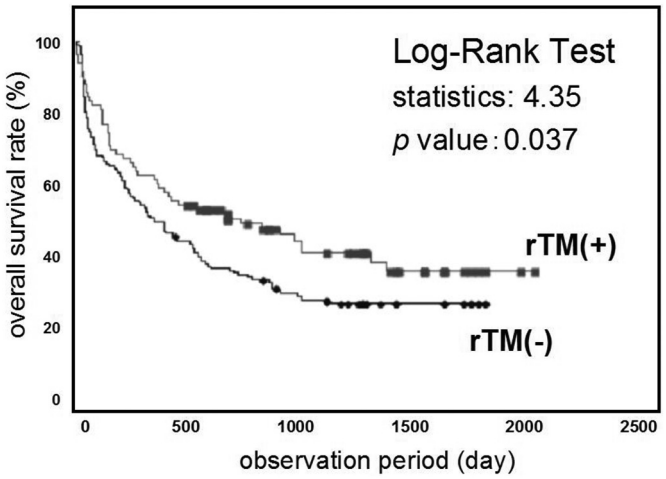

Fig. 1. Kaplan-Meier curves for overall survival of patients with or without rTM treatment.
rTM: recombinant thrombomodulin.

There are many causes of HSCT-related complications [7]. It is thought that mobilization of cells expressing various cytokines is a major cause. Cytokines increase after conditioning and cause intractable disease in the worst-case scenario, and the resulting tissue damage progresses [10]. This process affects the progression of GVHD. HMGB1 is particularly important for the immune cell mobilization after a conditioning regimen [13,18]. HMGB1 is expressed in blood vessel and causes tissue damage [24]. In our previous reports, we suggested that HMGB1 causes the onset of TMA and GVHD [18]. HMGB1 is regulated by TM on the blood vessel endothelium, and its serum concentration decreases over time [28]. The processing by the membrane type TM is beyond the tolerance level when a large quantity of HMGB1 is expressed [29]. In addition, in the case of the qualitative and/or quantitative obstacle of the membrane type TM, there are similar results. We suggest the possibility of preventing the insufficient regulation of HMGB1 by membrane-type TM through administration of rTM based on our previous study [18] We believe that some causes of a poor prognosis are aGVHD and TMA. The present findings suggest that rTM can prevent transplant-related complications, such as aGVHD and TMA, after allogeneic HSCT.

Declaration of Competing Interest

The authors do not have any conflicts of interest to report for this work.

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Table 1
Changes in various factors after HSCT with or without rTM.

rTM (−)($N = 169$)		rTM(+)($N = 131$)	Point estimate	95% CI	p value
Complication after HSCT					
aGVHD (Any Grade)	107(63%)	40 (31%)	42%	(−52.9%, − 31.2%)	< 0.0001
aGVHD (Grade II-IV)	89(53%)	27 (21%)	40%	(−50.8%, − 29.3%)	< 0.0001
VOD	15 (9%)	7 (5%)	42%	(− 11.2%, 1.7%)	0.1559
TMA	40(24%)	10 (8%)	20%	(−28.5%, − 11.0%)	< 0.0001
Survival at Day 100					
Dead	55(33%)	20 (15%)	16%	(− 25.9%, − 5.8%)	0.0036

N: number of patients; HSCT: hematopoietic stem cell transplantation; aGVHD: acute graft-versus-host disease; VOD: veno-occlusive disease; TMA: thrombotic microangiopathy; rTM: recombinant thrombomodulin; CI: cumulative incidence.

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