Can recombinant thrombomodulin play a preventive role for veno-occlusive disease after haematopoietic stem cell transplantation?

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Dear Sirs,

Although haematopoietic stem cell transplantation (HSCT) is being used for haematopoietic reconstitution following high-dose chemotherapy for malignancy, it involves some serious transplant-related complications (1, 2), such as graft-versus-host disease (GVHD) and vascular disorders (such as veno-occlusive disease (VOD), pulmonary vasculopathy, thrombotic microangiopathy (TMA), and capillary leak syndrome) (3–5). The authors have advocated “SIGHT” as a keyword for the complications after HSCT. This acronym comprises the capital letters of five complications after HSCT, namely sinusoidal obstruction syndrome (SOS same as VOD), Infection, GVHD, haemophagocytic syndrome (HPS) and TMA. In particular, VOD and TMA are involved in abnormalities of the haemostasis and coagulation system.

Injury to sinusoidal endothelial cells and hepatocytes by chemotherapy appears to be the primary event in the pathogenesis of VOD (6, 7). A number of markers for endothelial injury and adhesion molecules are upregulated in patients with VOD, including plasma thrombomodulin (TM), E-selectin, tissue factor, tissue factor pathway inhibitor and plasminogen activator inhibitor (8). Consequently, some biomarkers of endothelial injury are essential for predicting the development of VOD (9).

On the other hand, heparin is often used for the prevention of VOD, since it is an anticoagulant therapy (10). However, in a previous report by the authors, elevation of soluble (s) E-selectin and sVCAM-1 was observed despite heparin administration to prevent VOD after HSCT (11). Therefore, heparin may be inadequate for the prevention of VOD. In the present study, we measured sE-selectin and sVCAM-1 after HSCT using recombinant (r) TM (12, 13) instead of heparin. In addition, tumour necrosis factor (TNF)-α, high mobility group box 1 (HMGB1) and interleukin (IL)-6 were measured. To the best of our knowledge, no other investigators have measured these markers before and after rTM treatment in patients with allogeneic HSCT.

This study involved 12 patients (4 acute myeloid leukemia, 3 myelodysplastic leukaemia, 2 adult T-cell leukemia and 3 others) who underwent HSCT at the institution of residence, all of whom received allogeneic HSCT. The sources of donor tissue were three bone marrow transplantations, four peripheral blood HSCTs and five cord blood transplantations. RTM, consisting of daily doses of 380 units/kg (Asahi Kasei Pharma, Tokyo, Japan) was administered as a preventive therapy for VOD. This protocol was completed 7–21 days after HSCT. An anticoagulation regimen (5,000 U heparin 24 hours/day) was used prior rTM. Heparin was also administered to the Control group. Prior approval was obtained from the ethics review boards of all the participating institutions. Written informed consent was also obtained from all patients prior to rTM therapy.

As shown in Table 1, all the cytokines and soluble factors exhibited significant elevations on day 0 after HSCT. In addition, IL-6 and TNF-α exhibited more significant elevations on days 4–7 after HSCT (before rTM treatment). However, the levels of HMGB1, sE-selectin and sVCAM-1 did not exhibit significant changes on days 4–7. Significant improvements in IL-6, TNF-α and HMGB1 levels were noted after rTM treatment, but not after heparin treatment. In contrast, the levels of sE-selectin and sVCAM-1 did not show significant changes after rTM treatment. However, heparin...
Our results suggest that rTM treatment after allogeneic HSCT may prevent VOD. Several approaches have been evaluated for the treatment of VOD, but none has been uniformly effective (14). One of the most promising agents as a therapy for VOD is defibrotide, a novel polyoxymethylene oligonucleotide with adenosine receptor agonist activity (15). The results from a multi-institutional study have confirmed the benefits of this agent in therapy for established VOD (16). However, one of the action mechanisms of this agent depends on increased of TM on the endothelial surface (17, 18). In these cases, rTM exhibited a suppressive effect on the weight gain that is characteristic of cases, rTM is effective for certain complications of TM on the endothelial surface (17, 18). However, we recently observed high levels of rTM treatment. We were unable to document VOD in the patients before rTM treatment in this study. Therefore, we do not have any direct evidence to suggest that rTM actually prevented VOD. In addition, the decrease in sE-selectin and sVCAM-1 levels do not necessarily suggest a preventive effect for rTM. However, we recently observed high levels of rTM and sVCAM-1 in a patient with VOD (unpublished data). The aetiology of VOD remains unclear; although we believe one of the causes of VOD to be pro-inflammatory cytokines, such as HMGB1 (21, 22). For this reason, it is thought that the direct anti-inflammatory effect mediated via the rTM lectin domain plays an important role in preventing VOD. The present findings suggest the possibility that rTM can play a preventive role for VOD after allogeneic HSCT. However, there are still many unclear points regarding the therapeutic effects of rTM shown in “SIGHT”, including the action mechanism. Further studies using more patients and a revised protocol are required to further elucidate the mechanism by which rTM prevents VOD.

Conflict of interest
None declared.

Table 1: Changes in the levels cytokines and soluble factors after HSCT.

<table>
<thead>
<tr>
<th>Cytokine/factor</th>
<th>Before HSCT (preconditioning)</th>
<th>After HSCT - day 7</th>
<th>After HSCT day 0</th>
<th>After HSCT day 4 – 7 (before rTM)</th>
<th>After HSCT day 10 – 14 (after rTM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>rTM (n=12)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-6 (pg/ml)</td>
<td>18 ± 5</td>
<td>108 ± 57</td>
<td>127 ± 39</td>
<td>66 ± 22**</td>
<td></td>
</tr>
<tr>
<td>TNF-α (pg/ml)</td>
<td>13 ± 8</td>
<td>29 ± 11</td>
<td>78 ± 24</td>
<td>36 ± 19*</td>
<td></td>
</tr>
<tr>
<td>HMGB1 (IU/ml)</td>
<td>5.4 ± 0.7</td>
<td>21.4 ± 2.2</td>
<td>20.3 ± 1.7</td>
<td>10.1 ± 2.0**</td>
<td></td>
</tr>
<tr>
<td>sVCAM-1 (pg/ml)</td>
<td>988 ± 62</td>
<td>1,233 ± 74</td>
<td>1,292 ± 135</td>
<td>1,306 ± 119NS</td>
<td></td>
</tr>
<tr>
<td>sE-selectin (ng/ml)</td>
<td>61 ± 7</td>
<td>83 ± 5</td>
<td>84 ± 11</td>
<td>76 ± 9 NS</td>
<td></td>
</tr>
<tr>
<td>Heparin (n=5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-6 (pg/ml)</td>
<td>21 ± 7</td>
<td>93 ± 42</td>
<td>120 ± 46</td>
<td>119 ± 55 NS</td>
<td></td>
</tr>
<tr>
<td>TNF-α (pg/ml)</td>
<td>12 ± 3</td>
<td>25 ± 11</td>
<td>69 ± 28</td>
<td>71 ± 21 NS</td>
<td></td>
</tr>
<tr>
<td>HMGB1 (IU/ml)</td>
<td>5.1 ± 1.2</td>
<td>23.6 ± 9.9</td>
<td>24.5 ± 6.7</td>
<td>23.7 ± 6.2 NS</td>
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</tr>
<tr>
<td>sVCAM-1 (pg/ml)</td>
<td>956 ± 63</td>
<td>1,173 ± 164</td>
<td>1,325 ± 124</td>
<td>1,602 ± 301*</td>
<td></td>
</tr>
<tr>
<td>sE-selectin (ng/ml)</td>
<td>65 ± 10</td>
<td>79 ± 12</td>
<td>98 ± 21</td>
<td>119 ± 30 NS</td>
<td></td>
</tr>
</tbody>
</table>

Data represent the means ± standard error. IL-6: interleukin 6; TNF-α: tumour necrosis factor-α; HMGB1: high mobility group box protein 1; sVCAM-1: soluble vascular cell adhesion molecule-1; sE-selectin: soluble E-selectin. Statistical analysis exhibit */Before HSCT* vs. */After HSCT (day 0)*: **p < 0.001; ***p < 0.01; "Before rTM" vs. "/After rTM": ∗p < 0.01; ∗∗p < 0.05; NS: not significant.

References
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Letters to the Editor


