Thalidomide for Hereditary Hemorrhagic Telangiectasia With Pulmonary Arterial Hypertension

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A 37-year-old woman with a known diagnosis of pulmonary arterial hypertension (PAH; Table, January 1993) associated with hereditary hemorrhagic telangiectasia (HHT) and activin A receptor type II-like 1 (ACVRL1) mutation at the age of 17 years presented for repeated blood transfusions for the progressive anemia derived from recurrent epistaxis, hematemesis, tarry stool and melena. Telangiectasias were noted in the oral cavity (Figure A-1,B, arrows). Gastrointestinal scintigraphy (99mTc-human serum albumin diethylene-triamine-penta-acetic acid) showed extensive hemorrhage throughout the small and large intestines (Figure C, arrows). Chest X-ray showed hilar widening and cardiomegaly (Figure D). Electrocardiography and echocardiography indicated significant right ventricular overload (Figure E,F). Because beraprost 60 µg daily or bosentan 125 mg daily or ambrisentan 10 mg daily worsened the anemia, the patient was treated with 5 mg ambrisentan for PAH thereafter. The requirement for blood transfusion, however, increased year by year (Figure G). In 2013, the patient was urgently hospitalized for progressive anemia due to uncontrollable lower gastrointestinal oozing bleeding documented on video capsule endoscopy. Cardiac catheterization in February 2013 showed severe PAH with mean pulmonary arterial wedge pressure 10 mmHg, pulmonary arterial pressure (PAP), 97/40 mmHg (mean, 60 mmHg); and cardiac index 2.43 L/min/m² (Table). Her condition deteriorated even after repeated blood transfusions. Therefore, we decided to initiate thalidomide, which increases platelet-derived growth factor-B expression and downregulates vascular endothelial growth factor in endothelial cells, stimulating mural cell coverage and leading to normal vascular maturation.1,2 After the initiation of thalidomide (50 mg daily), the anemia was dramatically improved without blood transfusion (Figure H) and telangiectatic lesions in the tongue were no longer notable (Figure A-2). Although intensive therapy with pulmonary vasodilators might induce bleeding, we were able to add tadalafil 10 mg daily and increase ambrisentan to 7.5 mg daily without any bleeding side-effects. Twelve months after thalidomide treatment, right heart failure developed with deteriorating pulmonary hemodynamics (mean PAP, 90 mmHg; cardiac index, 1.88 L/min/m²; Table, January 2014). Wedged distal pulmonary angiography showed markedly decreased peripheral vessels (Figure I-2) as compared with that before thalidomide therapy (Figure I-1). After the discontinuation of thalidomide, the bleeding recurred and PAH did not improve, as reflected by serial changes in B-type natriuretic peptide and tricuspid regurgitation pressure gradient (Figure G,H). Finally, the patient died due to right heart failure. Thalidomide was beneficial against mucocutaneous bleeding,1,7 but careful consideration is required with regard to its initiation in HHT patients with PAH.

Disclosures
The authors declare no conflicts of interest.

Table. Hemodynamic Parameters

<table>
<thead>
<tr>
<th>Year</th>
<th>PAP (mmHg)</th>
<th>PVR (Wood units)</th>
<th>CI (L/min/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1993 January</td>
<td>76/36 (mean=52)</td>
<td>7.2</td>
<td>3.6</td>
</tr>
<tr>
<td>2013 February</td>
<td>97/40 (mean=60)</td>
<td>13.4</td>
<td>2.43</td>
</tr>
<tr>
<td>2014 January</td>
<td>139/70 (mean=90)</td>
<td>27.7</td>
<td>1.88</td>
</tr>
</tbody>
</table>

CI, cardiac index; PAP, pulmonary arterial pressure; PVR, pulmonary vascular resistance.

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**Figure.** (A,B) Multifocal oral vasodilatation findings. (A-1,B) Arrows, oral telangiectasia before thalidomide therapy. (A-2) Telangiectatic lesions in the tongue are not visible after the initiation of thalidomide. (C) Gastrointestinal scintigraphy ($^{99m}$Tc-human serum albumin diethylene-triamine-penta-acetic acid, 740 mBq). Arrows, extensive hemorrhage throughout the small and large intestines. (D) Chest X-ray showing hilar widening and cardiomegaly. (E,F) Electrocardiography and echocardiography indicating significant right ventricular overload. (G) No. red blood cell transfusions per year from 2005 until 2013. (H) No. red blood cell transfusions per month in 2013. Blood transfusion was reduced after the initiation of thalidomide. Although thalidomide was discontinued, pulmonary arterial hypertension did not improve according to serial changes in B-type natriuretic peptide (BNP) and tricuspid regurgitation pressure gradient (TRPG). (I) Pulmonary angiography (I-1) before and (I-2) after initiation of thalidomide. Arrows, peripheral vessels.
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References


