Plasma Exchange for Thrombotic Thrombocytopenic Purpura Following Hematopoietic Stem Cell Transplantation

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Abstract

A 17 years old female diagnosed with acute myeloid leukemia (AML)-M2 received an allogeneic haematopoietic stem cell transplant (HSCT) and was given graft versus host disease (GVHD) prophylaxis with methotrexate, cyclosporin-A (CsA) and methyl prednisolone. On day +42 post-transplant, she was diagnosed to have thrombotic thrombocytopenic purpura (TTP). Therapeutic plasma exchange (TPE) (40 ml/kg body mass) using fresh frozen plasma was performed on 8 consecutive days. The renal function, LDH levels, platelet count and peripheral smear findings improved but the neurological symptoms persisted even after TPE. Few reports are available in literature on the effectiveness of therapeutic plasma exchange (TPE) in post-bone marrow transplant (BMT) TTP. The good hematologic response achieved in this patient suggests that TPE could be life-saving and should be tried in every patient with post-BMT TTP. ©

INTRODUCTION

Thrombotic thrombocytopenic purpura (TTP) following BMT has been reported to occur in upto 13% of patients undergoing BMT. The pathogenesis and etiology of TTP in BMT patients may be related to endothelial cell damage due to total body irradiation (TBI) or treatment with cyclosporine-A (CsA). Unlike idiopathic TTP where TPE is the treatment of choice, TPE was not found to be effective in the management of TTP following BMT.1 We describe a patient of post-BMT TTP who showed hematological improvement following TPE, though the neurological manifestations of acute transverse myelitis (ATM) persisted.

CASE REPORT

A 17 year old female, diagnosed with AML-M2 received an allogeneic HSCT from a 100% HLA-matched sibling donor. The HSC harvest had a mononuclear cell (MNC) count of 3.71x10^8/kg body weight of the patient and a CD34+ cell count of 7.06x10^6/kg body weight of patient. Methotrexate, CsA and methylprednisolone were given for GVHD prophylaxis. The patient had continuous fever, mucositis and persistent vomiting since day +7 and her blood culture showed presence of E. coli for which appropriate antibiotics were started. Gut GVHD was diagnosed on day +14 and skin GVHD developed on day +21. Patient’s BUN levels increased upto 122 mg/dl and she had progressive thrombocytopenia (platelet count 25x10^9/L) alongwith the appearance of fragmented RBCs (>10%) on the peripheral smear. She also developed sudden onset acute sensorimotor flaccid paraparesis with bladder involvement and her lactate dehydrogenase levels (LDH) rose to 4292 U/L on day +42. During this period her serum CsA level was 346.9 ng/ml (Normal range 75 to 325 ng/ml). She was diagnosed to have post-HSCT TTP based on the above findings.

IVIg and methyl prednisolone was given and TPE using FFP as replacement fluid was immediately instituted. TPE (40 ml/kg body weight of the patient) was performed on a daily basis for 8 consecutive days on the CS3000 Plus Cell Separator, Baxter, Deerfield, IL, USA. The patient’s renal function and hematological parameters, including platelet count and LDH levels improved and remained stable after TPE, as shown in Table 1, though her neurological symptoms persisted.

The patient’s platelet count was always above 77,000/cumm in the post-TPE period. There were no signs of relapse of TTP in this period. On day 118 post-BMT, patient had fever with chills and rigors which did not respond to antibiotic therapy. Bone marrow aspiration performed on day 123 post-BMT to track the aetiology of this pyrexia showed presence of abundant trophozoites of Plasmodium falciparum. The patient did not respond to Quinine therapy and succumbed to
BMT associated TTP is an uncommon but fatal complication. The high risk form of TTP is found most commonly after allogeneic BMT in patients receiving CsA or fK506 for GVHD prophylaxis. It is often associated with other acute processes like infection, GVHD and has a high mortality rate despite aggressive therapy. The diagnosis of TTP is difficult in the setting of BMT and should be considered in any patient with unexplained hemolysis, a sudden increase in platelet transfusion requirements, renal failure or neurological symptoms after BMT. Van der Plas et al² suggest that a pathological condition called systemic inflammatory response syndrome (SIRS) may be involved in the pathogenesis of post-BMT TTP.

Pettitt and Clark¹ have recognized different clinical syndromes of post-BMT TTP. According to their classification, our patient belongs to a high mortality group (upto 84% mortality) termed multifactorial fulminant thrombotic microangiopathy (MFTM). MFTM consists primarily of patients with two or more of the following risks factors:

a) Occurrence within 120 days after HSCT
b) Use of CsA or fK506

c) Presence of both renal and neurological symptoms

Our patient did not receive TBI for conditioning but was given CsA for GVHD prophylaxis, had both renal (elevated BUN and S. creatinine) and neurological manifestations and developed TTP within 120 days after HSCT. TPE is usually effective for primary TTP, but there are only a few reports of TPE being effective for the treatment of post-BMT TTP especially in the presence of infection.⁵ Our patient responded to TPE although she had E. coli infection.

Zeigler et al⁶ concluded from their study that BMT associated TTP is common following allogeneic BMT and the outcome is dependent on the grade of the BMT associated thrombotic microangiopathy (BMT-TM). Those with grade I-II BMT-TM generally have better outcome. In contrast those with grades III-IV BMT-TM have partial hematologic responses and poor outcome. Our patient had grade IV BMT-TM.

Van der Plas et al⁷ reported only partial hematologic improvement in patients of post-BMT TTP treated by TPE and also highlighted a high mortality rate due to infections and metabolic disturbances in these patients. The ineffectiveness of TPE in these cases can be attributed to the failure to diagnose TTP early in the disease course and the subsequent delay in instituting TPE for these patients. Earlier treatment with TPE might have been more effective.

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Table 1: Patient’s laboratory parameters before and after TPE

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Laboratory Parameter</th>
<th>Normal Range</th>
<th>Pre-TPE</th>
<th>Post-TPE (after 8 exchanges)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Platelet count (x10⁹/L)</td>
<td>150-400</td>
<td>25</td>
<td>73</td>
</tr>
<tr>
<td>2.</td>
<td>BUN (mg/dl)</td>
<td>8-23</td>
<td>122</td>
<td>27</td>
</tr>
<tr>
<td>3.</td>
<td>Creatinine (mg/dl)</td>
<td>0.6-1.2</td>
<td>1.4</td>
<td>0.6</td>
</tr>
<tr>
<td>4.</td>
<td>LDH (U/L)</td>
<td>100-225</td>
<td>4292</td>
<td>774</td>
</tr>
<tr>
<td>5.</td>
<td>Bilirubin (mg/dl)</td>
<td>0.1-1.2</td>
<td>3.38</td>
<td>1.13</td>
</tr>
<tr>
<td>6.</td>
<td>ALT (U/L)</td>
<td>4-36</td>
<td>68</td>
<td>13</td>
</tr>
<tr>
<td>7.</td>
<td>AST (U/L)</td>
<td>8-33</td>
<td>68</td>
<td>22</td>
</tr>
<tr>
<td>8.</td>
<td>Prothrombin time (sec) Test/Control</td>
<td>—</td>
<td>12.5/10.6</td>
<td>10.1/10.7</td>
</tr>
<tr>
<td>9.</td>
<td>PTTK (sec) Test/Control</td>
<td>—</td>
<td>62.4/24.5</td>
<td>23.4/24.2</td>
</tr>
<tr>
<td>10.</td>
<td>S. uric acid (mg/dl)</td>
<td>2.7-7.3</td>
<td>7.1</td>
<td>1.5</td>
</tr>
<tr>
<td>11.</td>
<td>Reticulocyte count</td>
<td>—</td>
<td>2.5%</td>
<td>1%</td>
</tr>
<tr>
<td>12.</td>
<td>Fibrin degradation product (FDP)</td>
<td>—</td>
<td>2 to 4</td>
<td>2 to 4</td>
</tr>
<tr>
<td>13.</td>
<td>Fibrinogen (mg/dL)</td>
<td>200 to 400</td>
<td>340</td>
<td>378</td>
</tr>
</tbody>
</table>

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Fig. 1: Follow-up of patient’s platelet counts after PBSCT.

Fig. 2: Follow-up of serum LDH level after PBSCT.
The very first case of successful treatment of post-BMT TTP by TPE was reported by Milone et al in 1998. This was a case of CML who developed TTP after receiving allogeneic BMT and responded following 19 TPEs using FFP as replacement fluid. In a recent case report by Plews et al, TTP after autologous BMT in a small child was successfully treated by TPE using cryosupernatant as replacement fluid. Zeigler et al have shown that a combination of cryosupernatant exchange with immunoadsorption using protein-A column is more effective than cryosupernatant or FFP alone as replacement fluid in post-BMT TTP cases.

Kolker et al have described the case of a young patient who developed manifestations of TTP 10 months after BMT with complete recovery following treatment with TPE, everyday for 30 days using FFP. Their experience suggests that TPE with FFP if initiated early in the disease course could be highly effective in high-grade post-BMT TTP.

In BMT-TM, TTP and DIC can be present in the same patient and is difficult to distinguish. However, in this case the fibrinogen and FDP levels were normal, thus ruling out the possibility of DIC. The PTTK was easily corrected after the first plasma exchange.

In our case, after performing 8 TPE procedures, which were started immediately after onset of symptoms, there was remarkable improvement in the liver and renal functions, platelet count and LDH levels. Hematologic response was achieved, but the patient’s neurological symptoms persisted.

We suggest that all BMT recipients should be monitored prospectively post transplantation for the development of BMT-TM by performing simple investigations like measurement of percentage of fragmented red blood cells on peripheral smear. Early intensive TPE should be tried in all patients with this life threatening disorder at least until more effective treatment is available.

**REFERENCES**

1. Pettitt AR, Clark RE. Thrombotic microangiopathy following bone marrow transplantation. *Bone Marrow Transplantation* 1994;14:495-504.

**Announcement**

The Office-bearers of API Tamil Nadu State Chapter (API - TNSC) elected for the year 2005.

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