Bone Marrow Transplantation Corrects the Splenic Reticuloendothelial Dysfunction in Sickle Cell Anemia

By Alina Ferster, Willem BuJan, Francis Corazza, Christine Devalk, Pierre Fondu, Michèle Toppet, Michel Verhas, and Eric Sariban

In sickle cell anemia (SCA), the loss of reticuloendothelial function is the result of vasoocclusive events occurring in the spleen. Such asplenia occurs early in the course of the disease and is considered to be permanent in late childhood. In this report, three patients 10, 11, and 14 years of age suffering from severe SCA and found to be asplenic were treated by bone marrow transplantation (BMT). Before transplantation, all three patients had loss of reticuloendothelial splenic function, as assessed by the presence of abundant Howell-Jolly bodies on blood smears and absence of technetium 99m (99mTc) splenic uptake. After BMT, Howell-Jolly bodies disappeared from blood smear, whereas 99mTc isotopic scan found normal isotope uptake. Our data indicate that BMT can correct “permanent asplenia” in SCA patients. However, it remains to be determined if such treatment can also correct other SCA-related organ dysfunctions.

THE CLINICAL COURSE in sickle cell anemia (SCA) is still marked by a high morbidity rate and increased mortality rate in early adulthood.

Recently, allogenic bone marrow transplantation (BMT) has been investigated as a curative treatment in SCA. In our institution, patients having developed severe SCA-related events were considered for BMT. Although results of the first transplants are encouraging, controversy still surrounds this modality of treatment approach. In addition, it remains to be determined if such an approach might reverse organ damage resulting from the underlying disease.

Functional asplenia is known to develop early in SCA patients and contribute to disease morbidity and mortality. Most patients are considered as permanently asplenic when they reach the age of 7 years.

We have studied the splenic function in three patients with SCA and have found reversal of such functional asplenia after BMT.

PATIENTS AND METHODS

Since November 1988, seven children with SCA, aged 2 to 14 years, were selected for BMT in our institution and were treated according to a previously described protocol. Approval was obtained from the Institutional Review Board for these studies. Informed consent was provided according to the Declaration of Helsinki.

The three oldest patients (aged 10, 11, and 14 years) were carefully investigated for splenic function before and after BMT. Table 1 summarizes the clinical symptoms presented by the three patients before BMT.

May-Grünwald-Giemsa–stained blood films were examined for the presence of Howell-Jolly bodies before and after BMT. The technetium 99m (99mTc) sulfur colloid was prepared with particles of 0.2 to 1 μm in diameter (Ablu-Res; Solco Nuclear, Sorin Biomedica, Italy). 99mTc emits a monoeenergetic gamma ray and its half-life is short (6 hours). Thirty minutes after the injection of 185 MBq (equal to 5 mCi) of Albu-Res, four images (anterior, posterior, right lateral, left lateral) were taken in a supine position, with planar and scan camera (L.F.O.V. Siemens Camera, Germany). The scans were recorded on Polaroid films (RE 667).

RESULTS

All three patients engrafted successfully with acceptable early and late toxicity (Table 2). The actual follow-up ranges from 8 to 43 months. All three patients have now hemoglobin levels above 10 g/dL with electrophoretic pattern of donor type. Chromosome studies were noninformative because donor and recipient were of the same sex in each case. Since the time of transplantation, all three patients remain free of new SCA manifestations. Patient 1 developed a limited de novo chronic graft versus host disease (GVHD) that promptly responded to immunosuppressive therapy.

Before BMT, no patient had a palpable spleen. Repeated blood smear screenings in all three patients disclosed the presence of numerous Howell-Jolly bodies as well as sickled cells (Fig 1A). Hepatosplenic radionuclide 99Tc scintigraphy did not demonstrate splenic uptake (Fig 2A). Furthermore, prior to BMT, patients 2 and 3, suffering from symptomatic vesicular lithiasis, underwent surgery for cholecystectomy.

A careful screening of multiple blood smears 3, 6, and 12 months after BMT did not show the presence of Howell-Jolly bodies (Fig 1B). In patients 1 and 2, 99Tc hepatosplenic scintigraphy performed 1 and 1.5 years after BMT showed the presence of normal size splenic tissue (Fig 2C).

In patient 3, a hepatosplenectomy performed 3 months after BMT already showed the presence of splenic uptake (Fig 2B).

DISCUSSION

As previously reported by our group, we confirm that BMT in SCA is feasible, with a high cure rate. We and others did not see any mortality events related to the transplantation procedure. However, morbidity events such as opportunistic infections, hemorrhage, GVHD, graft rejection, lung fibrosis, infertility, or secondary tumors have to be expected. Long-term follow-up of our successful grafted patients shows...
Table 1. Selection Criteria for BMT

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age at BMT (yr)</th>
<th>Severe Repetitive Crises (1) or Acute Chest Syndrome (2)</th>
<th>No. of RBC Transfusions During Past Year</th>
<th>Stroke</th>
<th>Severe Alloimmunization</th>
<th>Karnovsky Score</th>
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<tr>
<td>1</td>
<td>10</td>
<td>1 (1)</td>
<td>12*</td>
<td>-</td>
<td>-</td>
<td>70</td>
</tr>
<tr>
<td>2</td>
<td>11</td>
<td>+ (1 and 2)</td>
<td>6</td>
<td>-</td>
<td>+</td>
<td>70</td>
</tr>
<tr>
<td>3</td>
<td>14</td>
<td>+ (1)</td>
<td>7</td>
<td>+</td>
<td>+</td>
<td>70</td>
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</table>

* Chronic transfusion support.

that they have a stable hemoglobin level and do not suffer from new SCA-related events.

Among the seven grafted patients, none developed acute GVHD, one developed a chronic GVHD, and two suffered from graft rejection. However, it remains to be determined if BMT can restore or improve the functions of organs severely damaged by the underlying disease. In this context, we studied splenic function in three patients.

Functional asplenia is defined as impaired splenic reticuloendothelial function. This inability to clear particules or microorganisms from blood develops early in the life of patients with SCA. Consequently, these patients are prone to develop microbial infections with a well-known increased risk of pneumococcal sepsis. Functional asplenia is classically defined by (1) the presence of Howell-Jolly bodies in circulating red cells and (2) the absence of reticuloendothelial splenic function, demonstrated by the disappearance of $^{99m}$Tc splenic uptake, even in the presence of a palpable spleen.

It was well demonstrated that functional asplenia may reverse after red blood cell (RBC) transfusion in young patients with palpable spleen. This reversible functional asplenia is explained by the fact that blood having a high viscosity bypasses the reticuloendothelial tissue of the spleen through intrasplenic shunts. However, by the age of 7, patients with SCA are considered as permanently asplenic despite RBC transfusions. At this age, most patients have a small fibrotic

Fig 1. Blood smear before (A) and after (B) BMT. Numerous sickled cells and Howell-Jolly bodies (arrow) present before BMT in patient 1 (A), have disappeared 3 months after BMT (B).
Fig 2. Hepatosplenic scintigraphy performed 30 minutes after injection of $^{99m}$Tc sulfur colloid (posterior projection). (A) Before BMT, $^{99m}$Tc scintigraphy in patient 3 shows a normal liver uptake. Splenic uptake is not detected even at higher exposure (lower scan). (B) Three months after BMT, splenic uptake previously absent (A) is detectable (arrow) (patient 3). (C) Twelve months after BMT, a normal spleen size with a normal uptake is demonstrated in patient 1.
Table 2. Long-Term Evaluation and Hematologic Parameters in Recipients Before and After BMT

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Follow-Up Duration (mo)</th>
<th>Karnovsky Score</th>
<th>Acute GVHD</th>
<th>Chronic GVHD</th>
<th>% HbS Before BMT</th>
<th>% HbS After BMT*</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>43</td>
<td>90</td>
<td>0</td>
<td>+ (limited de novo)</td>
<td>95</td>
<td>43</td>
</tr>
<tr>
<td>2</td>
<td>31</td>
<td>100</td>
<td>0</td>
<td>0</td>
<td>91</td>
<td>40</td>
</tr>
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<td>8</td>
<td>100</td>
<td>0</td>
<td>0</td>
<td>96</td>
<td>46</td>
</tr>
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</table>

* All marrow donors had sickle cell trait.

spleen (as seen at laparotomy in patients two and three). This "autosplenectomy" results from progressive vascular occlusion and infarction, and transfusion is not able to restore any more splenic function in this situation. We demonstrate here that, after BMT, permanent perfusion of the spleen with rheologically normal blood restores its size and its reticulo-endothelial function. The deficit is corrected early in the course of the BMT because patient 3 had functional splenic tissue detectable 3 months after BMT. Patients 1 and 2 were first tested 12 and 18 months after BMT and were found to have functional splenic tissue, as measured by 99mTc uptake, with normal spleen size.

Thus, in this study, we show for the first time that "permanent" organ damages resulting from vaso-occlusion can in fact be reversible after BMT in patients with SCA.

Careful investigation before and after BMT in the next SCA grafted patients should answer the question if organ damage secondary to ischemic vascular lesions in the eyes, kidney, brain, and lung is also reversible.

The results of these studies will be of critical importance to support the eventual role of BMT as a curative treatment in patients with SCA.

REFERENCES

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