RAPID COMMUNICATION

Neurologic Complications After Allogeneic Marrow Transplantation for Sickle Cell Anemia


Seven of 21 patients with sickle cell anemia developed neurologic complications 5 to 243 days (median 33 days) after allogeneic marrow transplantation. Among these 7 patients, indications for transplantation included either a past history of stroke (4 patients) or recurrent severe vaso-occlusive events (3 patients). All received marrow from an HLA-identical sibling after preparation with busulfan and cyclophosphamide, and in 4 patients with antithymocyte globulin. Five of 6 patients developing seizures received anticonvulsant and supportive treatment with resolution of neurologic abnormalities. Three patients experienced intracranial bleeding, which was fatal in two. Of the 14 patients free of neurologic complications, 4 patients had experienced stroke before transplantation. However, among all patients with prior stroke, the incidence of intracranial hemorrhage was 38% (3/8), whereas none of the 13 patients without prior stroke developed posttransplant intracranial bleeding (P = .026). We conclude that patients with sickle cell anemia are at increased risk for neurologic complications after marrow ablative therapy and that patients with prior stroke are at increased risk for intracranial hemorrhage. Transplantation of patients before the onset of overt stroke may reduce this risk.

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Marrow transplantation from HLA-identical siblings is effective therapy in children with nonmalignant disorders, including aplastic anemia, congenital immunodeficiency syndromes, thalassemia major, and certain inborn errors of metabolism.12 Its use in the treatment of sickle cell anemia has been limited to date but initial reports confirm that bone marrow transplantation is curative treatment for this disorder.12 Subsequent reports suggest that transplantation can be successfully applied to patients with symptomatic sickle cell disease, and initial data from European centers project an event-free survival of 86%.8,12

Improved outcome after marrow transplantation for hemoglobinopathies has been achieved, in part, by identifying patients earlier in the course of disease before organ damage has developed.13 A recent report showed a disease-free survival of 93% among 64 “good-risk” patients with thalassemia after transplantation from HLA-identical siblings.14 Based on these encouraging results in patients with thalassemia, a collaborative study is in progress to study the outcome of transplantation in symptomatic patients with sickle cell anemia. As part of the safety monitoring in this patient population, we report the neurologic complications observed in 7 patients after marrow transplantation. We speculate that pretransplant cytoreductive therapy may accelerate progression of pre-existing neurovascular damage in stroke patients with sickle cell anemia undergoing allogeneic marrow transplantation.

MATERIALS AND METHODS

Patients less than 16 years of age with symptomatic sickle cell anemia and organ dysfunction who had an HLA-identical sibling (hemoglobin genotype AA or AS) were considered for transplantation. Criteria for transplantation included prior history of a neurologic complication (stroke, hemorrhage, or neurologic defect lasting >24 hours), abnormal cerebral imaging or angiogram with impaired neuropsychologic testing, stage I-II sickle cell lung disease, sickle cell nephropathy with moderate to severe proteinuria or glomerular filtration rate of 30% to 50% predicted normal, visual impairment with bilateral proliferative retinopathy, acute chest syndrome with recurrent hospitalization or prior exchange transfusion, osteonecrosis of multiple joints, chronic debilitating pain with three or more episodes per year for several years, priapism, or chronic transfusion treatment with development of alloimmunization (>2 antibodies). Patient no. 1, transplanted at the University of Chicago, was 19 years of age but eligible for treatment at that institution. Detailed informed consent was obtained from each patient or guardian before study entry.

Patients were prepared for transplantation with a combination of busulfan and cyclophosphamide. Busulfan doses ranged from 14 to 18 mg/kg. All patients received 200 mg/kg cyclophosphamide over 4 days and three also received antithymocyte globulin. Five patients received a combination of methotrexate and cyclosporine A (CSP) for prevention of graft-versus-host-disease (GVHD). The other two patients received CSP alone or in combination with prednisone.

Exact tests were calculated for statistical comparisons of proportions of patients with neurologic complications using small sample computer simulations.15

RESULTS

Patient characteristics. Seven patients who experienced neurologic complications received grafts between November

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Table 1. Patient and Transplant Characteristics

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age</th>
<th>Sex</th>
<th>Donor Hemoglobin Genotype</th>
<th>Indication for Transplant</th>
<th>Pretransplant Neurologic Status: Clinical/Imaging</th>
<th>Preparative Regimen</th>
<th>GVHD Prophylaxis</th>
<th>Acute GVHD Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>19 yr</td>
<td>F</td>
<td>AA</td>
<td>Stroke</td>
<td>History of seizure with rt. hemiparesis/bilateral MCA occlusion with watershed infarction/ Moye-moya</td>
<td>Bu (16) + CY (200)</td>
<td>MTX + CSP</td>
<td>Gr I</td>
</tr>
<tr>
<td>2</td>
<td>5 yr 6 mo</td>
<td>M</td>
<td>AS</td>
<td>Recurrent VOC</td>
<td>Normal exam with no history of dysfunction/ none performed</td>
<td>Bu (16) + CY (200)</td>
<td>MTX + CSP</td>
<td>Gr I</td>
</tr>
<tr>
<td>3</td>
<td>13 yr 2 mo</td>
<td>F</td>
<td>AS</td>
<td>Recurrent VOC</td>
<td>Normal exam with no history of dysfunction/ normal cranial CT</td>
<td>Bu (18) + CY (200) + ATG (80)</td>
<td>MTX + CSP</td>
<td>Gr III</td>
</tr>
<tr>
<td>4</td>
<td>6 yr 7 mo</td>
<td>F</td>
<td>AS</td>
<td>Recurrent VOC</td>
<td>Normal exam with no history of dysfunction/ none performed</td>
<td>Bu (16) + CY (200)</td>
<td>CSP</td>
<td>Gr I</td>
</tr>
<tr>
<td>5</td>
<td>10 yr</td>
<td>F</td>
<td>AS</td>
<td>Stroke</td>
<td>History of left hemiplegia and seizure/right MCA occlusion with watershed infarction</td>
<td>Bu (14) + CY (200) + ATG (90)</td>
<td>MTX + CSP</td>
<td>None</td>
</tr>
<tr>
<td>6</td>
<td>10 yr 6 mo</td>
<td>F</td>
<td>AA</td>
<td>Stroke</td>
<td>History of rt. hemiparesis and aphasia/left MCA occlusion with watershed infarction</td>
<td>Bu (14) + CY (200) + ATG (90)</td>
<td>MTX + CSP</td>
<td>Gr I</td>
</tr>
<tr>
<td>7</td>
<td>11 yr</td>
<td>M</td>
<td>AS</td>
<td>Stroke</td>
<td>History of seizure with coma/micorvascular abnormalities in occipital lobes</td>
<td>Bu (16) + CY (200) + ATG (80)</td>
<td>Pred + CSP</td>
<td>Gr I</td>
</tr>
</tbody>
</table>

Abbreviations: ATG, antithymocyte globulin; Bu, busulfan; CY, cyclophosphamide; Gr, grade; MCA, middle cerebral artery; MTX, methotrexate; Pred, prednisone; VOC, vaso-occlusive crisis.

25, 1988 and January 29, 1993 among a total of 21 transplant recipients (16 in France and 5 in the United States) with sickle cell anemia. As shown in Table 1, the 7 patients ranged in age from 5.5 to 19 years (median, 10.5 years). Five had narrow donors of AS hemoglobin genotype and two patients had AA genotype donors. Indications for marrow transplantation included prior stroke (N = 4) and frequent vaso-occlusive crises (N = 3). Patients with a history of stroke ranged in age from 10 to 19 years. All were previously managed for 1.5 to 7 years with red blood cell transfusions to maintain an Hb S fraction less than 30%. Three patients had radiographic evidence of cerebral infarction with intracerebral vascular disease involving major vessels; the fourth patient (patient no. 7) had evidence of microvascular neurologic disease. Neuropsychologic testing was performed before transplantation in three patients and was abnormal in two. Pretransplant neurologic examination was abnormal in only one patient with a history of stroke (patient no. 1). None of the three patients with recurrent vaso-occlusive crises had previous history of neurologic events, and all had normal neurologic exams.

Fourteen of the 21 patients did not experience neurologic complications after transplantation. Four of these 14 patients experienced stroke before transplantation (Table 2). Although screening neuroimaging studies were not performed in all 14 patients, among the 10 patients without prior stroke, neuroimaging studies were normal with the exception of a single patient with an abnormal transcranial doppler study and normal cerebral magnetic resonance imaging/magnetic resonance angiography (MRA/MRA). In addition, these 14 patients did not differ in age or experience GVHD at a different rate from those patients with neurologic complications, but did appear to have fewer hypertensive episodes (Table 2). Indications for transplantation among the 10 patients without prior stroke included frequent vaso-occlusive crises (N = 10), recurrent acute chest syndrome (N = 7), and osteonecrosis (N = 3).

Posttransplant neurologic events. The overall incidence of neurologic complications after transplantation was 50% (4/8) in patients with prior stroke and 23% (3/13) in those without prior stroke (P = .5). Seizures were the most common complication (Table 3). With one exception, these occurred early after transplantation, generally within the first 30 days. Hypertension was present in 4 of 6 patients with seizures in whom systolic pressures ranged from 140 to 200 mmHg and diastolic pressures from 96 to 120 mmHg, whereas only 1 of the 14 patients without neurologic complications was hypertensive (Table 2). In addition, it was observed that 3 of 7 patients who experienced neurologic events after transplantation were thrombocytopenic and 3 of 7 were relatively polycythemic for patients with sickle cell disease. Seizure management included institution of anticonvulsants, discontinuation of CSP, and administration of antihypertensive agents. CSP was subsequently resumed in all cases and

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patients were maintained on therapeutic levels of anticonvulsants. Control of hypertension was achieved with administration of nifedipine, atenolol, and/or hydralazine. One patient (patient no. 6) experienced a second episode of seizures when she became hypertensive with subtherapeutic plasma levels of phenytoin. Once adequate levels of anticonvulsants were restored, the seizures resolved. Patient no. 5 developed headache and hypertension on day 7 posttransplant and 24 hours later experienced generalized tonic-clonic seizures. A cerebral computed tomography (CT) scan showed diffuse subarachnoid hemorrhage most prominent in the left paramesencephalic cistern with increased ventricular size. The platelet count had been less than 10,000/μL despite support with random donor platelet transfusions. With control of hypertension, initiation of anticonvulsant therapy, and addition of nifedipine, atenolol, and/or hydralazine, one patient experienced a second episode of seizures. Neuro-imaging studies documented bilateral watershed infarction and MRA showed occlusion of both internal carotid arteries, with flow voiding in the region of the posterior corpus callosum and abundant collateral vasculature, consistent with Moya-moya disease. Hypertransfusion therapy was resumed and referral was made for marrow transplantation (Table 3). The incidence of intracranial hemorrhage in patients with prior stroke was 38% (3/8), compared with 0 of 13 patients without prior stroke (P = .026). Mortality from neurologic complications was 25% among patients with prior stroke and there were no deaths from a neurologic complication among patients without prior stroke (P = .08). Two patients with intracranial hemorrhage died and their course is summarized below.

Case reports. Patient no. 1 experienced multiple cerebral vascular accidents beginning at 2 years of age and was managed on a transfusion program for 6 years. After discontinuation of transfusions, she remained symptom free for 7 years, at which time she developed headache, followed by right focal seizures. Neuro-imaging studies documented bilateral watershed infarction and MRA showed occlusion of both internal carotid arteries, with flow voiding in the region of the posterior corpus callosum and abundant collateral vasculature, consistent with Moya-moya disease. Hypertransfusion therapy was resumed and referral was made for marrow transplantation. Five days after transplantation, she

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age</th>
<th>Pretransplant Neuro-Imaging Studies</th>
<th>Prior stroke</th>
<th>Acute/Chronic GVHD (Gr)</th>
<th>Episodes of Hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>8 yr 7 mo</td>
<td>Abnormal cranial MRI/MRA</td>
<td>Yes</td>
<td>0/0</td>
<td>No</td>
</tr>
<tr>
<td>9</td>
<td>5 yr 10 mo</td>
<td>None performed</td>
<td>No</td>
<td>1/0</td>
<td>No</td>
</tr>
<tr>
<td>10</td>
<td>8 yr 9 mo</td>
<td>Normal cranial CT</td>
<td>No</td>
<td>11/11</td>
<td>No</td>
</tr>
<tr>
<td>11</td>
<td>11 yr 5 mo</td>
<td>Normal cranial CT</td>
<td>No</td>
<td>0/0</td>
<td>No</td>
</tr>
<tr>
<td>12</td>
<td>2 yr 8 mo</td>
<td>Normal cranial CT</td>
<td>No</td>
<td>0/0</td>
<td>No</td>
</tr>
<tr>
<td>13</td>
<td>9 yr 6 mo</td>
<td>None performed</td>
<td>No</td>
<td>0/0</td>
<td>No</td>
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<tr>
<td>14</td>
<td>14 yr 9 mo</td>
<td>Abnormal cranial CT</td>
<td>Yes</td>
<td>0/0</td>
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<tr>
<td>15</td>
<td>9 yr 7 mo</td>
<td>Normal cranial CT</td>
<td>Yes</td>
<td>0/0</td>
<td>No</td>
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<tr>
<td>16</td>
<td>8 yr</td>
<td>Abnormal cranial CT</td>
<td>Yes</td>
<td>0/0</td>
<td>No</td>
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<tr>
<td>17</td>
<td>10 yr 7 mo</td>
<td>None performed</td>
<td>No</td>
<td>0/0</td>
<td>No</td>
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<tr>
<td>18</td>
<td>2 yr 3 mo</td>
<td>None performed</td>
<td>No</td>
<td>0/0</td>
<td>No</td>
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<td>19</td>
<td>12 yr 8 mo</td>
<td>Normal cranial MRI/MRA</td>
<td>No</td>
<td>0/0</td>
<td>Yes</td>
</tr>
<tr>
<td>20</td>
<td>8 yr 4 mo</td>
<td>Abnormal TCD/normal cranial MRI</td>
<td>No</td>
<td>0/0</td>
<td>No</td>
</tr>
<tr>
<td>21</td>
<td>7 yr 10 mo</td>
<td>Abnormal TCD/abnormal cranial MRI/MRA</td>
<td>Yes</td>
<td>0/0</td>
<td>Yes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Event</th>
<th>Day Posttransplant</th>
<th>CSP Level (ng/mL)</th>
<th>BP (mm Hg)</th>
<th>HgB (g/dL)</th>
<th>PLT (x10^9/μL)</th>
<th>Neuroimaging Study Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Seizure</td>
<td>5</td>
<td>650</td>
<td>116/76</td>
<td>8.3</td>
<td>44</td>
<td>Not changed from baseline</td>
</tr>
<tr>
<td></td>
<td>IVH</td>
<td></td>
<td>243</td>
<td>178</td>
<td>160/90</td>
<td>313</td>
<td>Cranial CT: rt. subdural hematoma, progressing to massive IVH</td>
</tr>
<tr>
<td>2</td>
<td>Seizure</td>
<td>18</td>
<td>759</td>
<td>200/100</td>
<td>11.4</td>
<td>170</td>
<td>Normal cranial CT</td>
</tr>
<tr>
<td>3</td>
<td>Seizure</td>
<td>225</td>
<td>200</td>
<td>190/100</td>
<td>13</td>
<td>300</td>
<td>Normal cranial CT, MRI</td>
</tr>
<tr>
<td>4</td>
<td>Seizure</td>
<td>30</td>
<td>132</td>
<td>140/—</td>
<td>11.4</td>
<td>148</td>
<td>Cranial CT: small right parietal hypodense lesion; spontaneously resolved 6 mo-later</td>
</tr>
<tr>
<td>5</td>
<td>Seizure, SAH</td>
<td>8</td>
<td>162</td>
<td>146/96</td>
<td>9.9</td>
<td>8</td>
<td>Cranial CT: diffuse SAH</td>
</tr>
<tr>
<td>6</td>
<td>Seizure</td>
<td>33</td>
<td>&lt;50</td>
<td>140/102</td>
<td>14.3</td>
<td>219</td>
<td>Stable cranial CT</td>
</tr>
<tr>
<td>7</td>
<td>Seizure</td>
<td>46</td>
<td>63</td>
<td>160/120</td>
<td>11.6</td>
<td>275</td>
<td></td>
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<tr>
<td>8</td>
<td>ICH</td>
<td>90</td>
<td>332</td>
<td>119/68</td>
<td>13.6</td>
<td>21</td>
<td>Cranial CT: massive ICH</td>
</tr>
</tbody>
</table>

Abbreviations: BP, blood pressure; HgB, hemoglobin; ICH, intracranial hemorrhage; IVH, intraventricular hemorrhage; nl, normal; PLT, platelet; SAH, subarachnoid hemorrhage.
developed right-sided focal seizures that resolved once therapeu-
tic plasma phenytoin levels were restored. The remainder of the immediate posttransplant course was unremarkable except for development of mild skin GVHD. Five months after transplantation, the patient developed hepatic function abnormalities and liver biopsy evidenced chronic GVHD, hemosiderosis, and cirrhosis. Immunosuppression with CSP and prednisone was resumed and chelation therapy was added. Hepatic function improved, but several weeks later she developed respiratory insufficiency. Bronchiolitis obliterans was suspected and CSP/prednisone doses were increased and azathioprine was added. She developed mild hypertension on corticosteroids and, while hospitalized, the patient complained of headache followed by loss of consciousness. A cranial CT showed a large right subdural hematoma. At the time of this event, the platelet count was 313,000/µL, prothrombin time (PT) was 13.0, partial thromboplastin time (PTT) was 25.6, and the fibrinogen level was 217 mg/dL. Although her clinical condition stabilized with subdural clot removal, 48 hours later she became unresponsive. A second cranial CT scan documented massive intraventricular hemorrhage and the patient died 243 days after marrow transplantation. Autopsy confirmed the hepatic processes and showed pulmonary lesions consistent with bronchiolitis obliterans. Fungal abscesses involving the left kidney and adrenal gland were noted with morphology consistent with mucormycosis. Permission to examine the brain was denied.

Patient no. 7 had evidence of pretransplant microvascular neurologic disease. Cerebral MRI showed demyelination of the left corona radiata and the centrum semiovale bilaterally with normal MRA. A positron emission tomography scan showed decreased cerebral glucose metabolism and reduced blood flow in the anterior superior frontal cortex, bilaterally, and in the right occipital cortex. Stationary photon emission imaging demonstrated defects in both anterior cerebral vessels and right occipital vessels and visual evoked potentials documented a severe postchiasmal lesion in the right occiput. Two months after transplantation, he experienced an episode of aphasia and confusion. Cerebral CT and MRI showed no significant changes and this event was attributed to hypertension because of CSP toxicity. Three months after transplantation, he developed thrombocytopenia with platelet counts ranging between 15,000 and 20,000/µL and required transfusion of HLA-matched platelets. The patient was subsequently found unconscious at home with fixed and dilated pupils. The platelet count was 21,000/µL, PT was 11.5, PTT was 29, and blood pressure and serum CSP levels were within normal limits. Cerebral CT imaging showed a massive intracerebral hemorrhage with involvement of the frontoparietal lobes and midline shift. He died 24 hours later and postmortem examination was not performed.

**DISCUSSION**

Indications for marrow transplantation in patients with sickle cell anemia remain incompletely defined. Ideally, candidates at risk for early morbidity and mortality from sickle vasculopathy would be identified before development of irreversible organ damage, thereby diminishing the risks associated with transplantation. Although unanimous agreement regarding indications for transplantation may not exist, most clinicians agree that patients with prior stroke should be considered for marrow transplantation. Stroke occurs in 6% to 12% of patients with sickle cell disease. Although blood transfusions are effective in preventing recurrent strokes, chronic transfusions can be associated with serious complications such as infection, red blood cell alloimmunization, and iron overload. There appears to be no treatment interval after which transfusions can be safely discontinued. One prospective study demonstrated subsequent recurrent strokes in 50% of patients transfused for 5 to 12 years. Moreover, even during chronic transfusion therapy, patients appear to be at increased risk for intracranial hemorrhage.

Initial reports from transplant centers in Belgium did not note an increase in neurologic complications after marrow transplantation for sickle cell anemia; however, only 2 of those 28 patients experienced overt stroke before transplantation. Three French patients with prior stroke reported here also did not experience neurologic complications after transplantation. However, these patients received marrow transplants within 6 months of the initial stroke, and posttransplant platelet counts were maintained to levels greater than 50,000/µL. F. Bernaudin, unpublished data). It is possible that adverse neurologic events may be reduced by augmenting supportive measures to prevent hemorrhage and seizures and by proceeding promptly to marrow transplantation before additional neurovascular damage has developed. Indeed, some experts have advocated early transplant for the asymptomatic child given the magnitude of morbidity and mortality associated with sickle cell disease.

The frequency of adverse neurologic events in the 21 patients with sickle cell anemia reported here is far higher than in other transplant recipients. Among 265 patients with aplastic anemia, paroxysmal nocturnal hemoglobinuria, or myelodysplastic syndrome from the Seattle series, only 10 (3.8%) patients experienced seizures and none developed intracranial hemorrhage more than 100 days after HLA-identical transplantation; even in a larger cohort of 895 patients with malignancy prepared for transplant with total body irradiation and intrathecal and intravenous chemotherapy, 21 (2.3%) experienced seizures and only 7 (0.8%) developed intracranial hemorrhage as a late complication (unpublished data). These results suggest that patients with sickle cell anemia are at increased risk for neurologic complications after marrow transplantation; in particular, patients with prior stroke are at increased risk for intracranial hemorrhage. Although the precise etiology of neurologic complications remains unclear, we speculate that pre-existing cerebral vasculopathy may predispose these patients to posttransplant complications. It has been previously noted that intracranial hemorrhage is frequent in sickle cell patients with prior cerebral infarction. In one report, patients ranging in age from 2 to 15 years at the time of cerebral infarction experienced intracranial hemorrhage at 14 to 39 years of age. The 3 patients with intracranial hemorrhage described in the present report ranged in age from 10 to 19 years, suggesting that therapy may have accelerated progression from cerebral...
infarction to intracranial hemorrhage. Another recent report described a fatal episode of intracranial hemorrhage in a 20-year-old patient with prior stroke who was receiving hydroxyurea treatment resulting in a 10-fold increase in fetal hemoglobin (HbF) levels to 30%. The investigators noted that increased HbF levels did not protect from progressive vascular damage and that chemotherapy did not stop progression of advanced cerebral vasculopathy.

Other factors may also contribute to neurologic complications in patients with sickle cell anemia undergoing transplantation. Neurotoxicity has been reported in 3% to 8% of marrow transplant patients receiving CSP for immunosuppression. CSP has been shown to lower the seizure threshold and has been associated with motor, spinal, and cerebellar-like syndromes and mental confusion. Seizures may be provoked by concomitant hypertension, hypomagnesemia, or hypcholesterolemia. Other neurologic findings in CSP recipients include tremors, paresthesias, encephalopathy, cortical blindness, paresis, and coma; however, several large series have not described intracranial hemorrhage associated with CSP administration. Thus, a recent observation from the Toronto group of intracranial hemorrhage in one patient with sickle cell anemia receiving CSP after orthotopic liver transplantation is also of considerable interest.

It is still too early to fully determine the benefits and risks of marrow transplantation for sickle cell anemia. Initial reports have shown the resolution of pain and morbidity from vaso-occlusive crises, an improvement in osteonecrosis, and a reversal of splenic reticuloendothelial dysfunction. For patients with other life-threatening hematologic diseases, the long-term quality of life after bone marrow transplantation has been reported to be excellent in cross-sectional and longitudinal studies. We have continued accrual of patients with prior stroke, but have instituted posttransplant supportive measures to prevent neurologic complications after transplantation; for patients with sickle cell anemia, further follow-up is needed to determine whether marrow transplantation can prevent late progression of cerebral damage. Extended duration of anticonvulsant prophylaxis and intensified antihypertensive management and platelet support may diminish the frequency of peritransplant seizures. Transplantation of patients before the development of stroke and overt cerebral vasculopathy will also be likely to decrease the risk of subsequent neurologic complications in patients with sickle cell anemia.

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Neurologic complications after allogeneic marrow transplantation for sickle cell anemia [see comments]

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