Treatment of Chediak-Higashi Syndrome by Allogenic Bone Marrow Transplantation: Report of 10 Cases

By Elie Haddad, Françoise Le Deist, Stéphane Blanche, Malika Benkerrou, Pierre Rohrlich, Etienne Vilmer, Claude Griscelli, and Alain Fischer

Chediak-Higashi syndrome is a rare condition characterized by susceptibility to bacterial infections, defective natural killer activity, and episodes of macrophage activation known as accelerated phases. Chemotherapy can induce transient remission of the accelerated phase, but relapses become less and less sensitive to treatment and ultimately lead to death. Allogenic bone marrow transplantation (BMT) has been proposed as a curative treatment for Chediak-Higashi syndrome. We report the outcome of BMT in 10 such children. Seven received marrow from an HLA-identical related donor and three from an HLA-nonidentical related donor. Three patients died, two from a new accelerated phase after rejection of transplanted bone marrow and one from cytomegalovirus (CMV) pneumonia. Six of seven recipients of HLA-identical marrow and one of three recipients of HLA-nonidentical marrow are alive and well without treatment 1.5 to 13 years after transplantation (median, 6.5 years). No manifestations of accelerated phases have occurred in these seven patients, and significant natural killer activity is detectable. Interestingly, BMT prevented recurrence of accelerated phases in patients with limited numbers of donor-type leukocytes after transplantation. Ocular and cutaneous albinism were not corrected after transplantation. None of the patients developed serious toxic reactions to the BMT conditioning regimen or have long-term sequelae. These results show that HLA-identical BMT is an acceptable curative treatment for Chediak-Higashi syndrome, whereas HLA-nonidentical BMT remains an experimental approach.

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Thrombocytopenia (<150,000/µL) and anemia (<10 g/dL) were

Once accelerated phases have occurred, the disease is invariably fatal before the use of etoposide (VP-16) combined with steroids and intrathecal methotrexate. However, remissions are transient, and relapses become increasingly insensitive to treatment; patients eventually die of bleeding complications and infections.

Bone marrow transplantation (BMT) has been proposed in these cases because it has been shown to revert the leukocyte disorder of beige mice, a model of CHS. There have been several reports of successful BMT in CHS patients with no recurrence of accelerated phases. We report the results of BMT in 10 children with CHS, emphasizing long-term outcome.

MATERIALS AND METHODS

Patients

We reviewed the cases of 10 consecutive patients with CHS who underwent a total of 12 allogenic BMTs in two centers (Hôpital des Enfants Malades or Hôpital Robert Debré, Paris, France). The diagnosis of CHS was based on an association of partial oculocutaneous albinism with characteristic findings, detection of enlarged granulations in blood leukocytes, and defective NK cell activity.

As shown in Table 1, age at diagnosis varied from 2 months to 10 years (median, 32 months). Age at BMT varied from 4 months to 126 months (median, 37 months). The median time between diagnosis and BMT was 7 months (range, 2 to 19 months). Diagnosis was facilitated by the following features: consanguinity (n = 7), presence of an affected sibling (n = 1), repeated bacterial infections (n = 4), and accelerated phases (n = 5). Hypopigmentation of the skin was noticed in all patients except patient 7, and thin hair with silvery tint was observed in all patients. Ocular symptoms including photophobia and/or hypopigmentation of iris and retina and/or nystagmus were noticed in all patients except patient 7. Three patients had severe neurologic manifestations, including blindness associated with abnormal chiasma on the chromatography (CT) scan, cerebellar ataxia (n = 1), and a slight delay in milestone acquisition (n = 2).

Neutropenia (less than 1,000/µL) was present in seven patients, and the five patients tested had reduced granulocyte chemotaxis. All patients had typical enlarged granulations in blood leukocytes.

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present in four patients (Table 2). Cytotoxic T-cell activity was reduced in four of four cases (data not shown). The activity of NK cells was profoundly decreased in all cases (see Table 4). Cases 1 through 4, 9, and 10 have previously been described in detail.\(^1\) Patient 7 was considered to have CHS because of the detection of typical granulations in blood leukocytes and thin hair with silvery tint, despite the absence of detectable ocular albinism.

The accelerated phase was defined as the association of persistent fever with hepatosplenomegaly, pancycopenia, low fibrinogen level, increased liver enzyme activity, and hypertriglyceridemia.\(^1\)\(^8\)\(^13\) Accelerated phase occurred in all patients before BMT except in patients 1 and 5. Patient 1 relapsed with an accelerated phase between the first and the second BMT. Accelerated phases were successfully treated by intravenous infusion of VP-16, steroids, and intrathecal methotrexate,\(^1\)\(^3\) although they recurred in two patients. Except for patient 4, BMT was performed in complete remission from an accelerated phase (Table 2). Accelerated phases were associated with Epstein-Barr virus (EBV) infection in patient 6 and Rickettsia conori in patient 8. In the seven other cases, no pathogen was detected.

**BMT**

**HLA-identical BMT.** Seven patients received nine marrow collections from HLA A,B,DR-identical, mixed lymphocyte reaction-negative siblings (n = 4) or parents (n = 3) (Table 2). Conditioning regimen consisted of VP-16 [300 mg/m\(^2\) intravenously (IV) on days -12 through -10], busulfan (4 mg/kg on days -9 through -6), and cyclophosphamide (Cy; 50 mg/kg on days -5 through -2), with the following exceptions. Patient 7 received a total dose of VP-16 of 400 mg/m\(^2\) before the first and second BMT; busulfan 20 mg/kg before the first BMT, and 26 mg/kg of busulfan and horse ATG before the second BMT. Patient 1 received only Cy (200 mg/kg total dose) before the first BMT and Cy (100 mg/kg total dose) and total body irradiation (7 Gy with lung shielding to 3.5 Gy) before the second BMT.\(^15\) VP-16 was added to the conventional busulfan/Cy regimen because of its efficacy in familial hemophagocytic lymphohistiocytosis, a syndrome analogous to CHS.\(^14\)\(^15\) presumptively due to its activity against activated lymphocytes and monocytes/macrophages.

Patient 2 received marrow T cell-depleted by E-rosetting. All other matched patients received unmanipulated marrow.

Graft-versus-host disease (GVHD) prophylaxis consisted of cyclosporine (3 mg/kg/d as a continuous IV infusion, then 3 mg/kg/d orally from day 60 for 6 months) combined with methotrexate (10 mg/m\(^2\) on days +1, 3, 6, and 11), except for in the case of patient 1, who received only methotrexate (days +1, 3, 6, and 11 and weekly until day 90).

**HLA-nonidentical BMT.** Three patients received HLA-nonidentical marrow from a single antigen-mismatched sibling (patients 8 and 10) or a haplotype-mismatched parent (patient 9) (Table 2). The conditioning regimen was the same as for recipients of HLA-identical marrow, except in the case of patient 10, who also received cytosine arabinoside (1 g/m\(^2\) at days -11 and -10, while VP-16 was given at days -14 through -12) because of persistent neurologic manifestations of an accelerated phase (presence of lymphoblasts). All nonidentical patients received marrow that was T cell-depleted by E-rosetting. Cyclosporine (3 mg/kg/d) was infused for 60 days. To prevent graft rejection, patient 8 also received two mouse monoclonal antibodies specific for lymphocyte function-associate antigen 1 (LFA-1; Pasteur Mérieux, Lyon, France) and CD2 (Innova, Besançon, France) by the IV route from days -3 through +10 (0.2 mg/kg/d).

All patients were placed in sterile isolators or laminar-air-flow rooms. They underwent gut decontamination by means of nonabsorbable antibiotics and received weekly IV infusions of Ig. Parents gave their informed consent to the procedure in every case. The last evaluation was made on December 31, 1993.
Laboratory Methods

Chimerism was assessed by determining the fraction of leukocytes with typical abnormal granulations on blood smears, immunoglobulin allotyping, erythrocyte phenotyping, HLA typing (when donor was HLA-incompatible), and the use of a Y chromosome-specific probe in Southern blot analysis (provided by Dr Drouard and Prof Nessman, Paris, France) or polymerase chain reaction (PCR) amplification of leukocyte DNA with microsatellite probes (provided by Prof Jeannet, Geneva, Switzerland).

NK activity was measured using K562 cells as targets in a 

RESULTS

Engraftment, Complications, and Outcome

**HLA-identical BMT.** Engraftment was achieved in six of seven HLA-identical transplants, after two attempts in patient 1 (probably because of insufficient conditioning). Despite the use of a conditioning regimen in patient 7 similar to that received by the other patients, stable engraftment could not be obtained, and he died 2 years later of accelerated phase (Table 3).

The kinetics of hematologic lineage development were remarkable in the patients who were successfully engrafted. The median day to an absolute neutrophil count (ANC) of greater than 500/μL was 22 days (range, day 17 to day 31); last platelet transfusion on day 25 (range, day 12 to day 50); last erythrocyte transfusion on day 27 (range, day 15 to day 40; Table 3).

No unusual toxicity of the conditioning regimen was noted. Mucositis was mild in all cases. Mild (grade I to II) and transient acute GVHD occurred in five patients; none developed chronic GVHD (Table 3). Bacterial and fungal

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**Table 2. BMT and Status of Disease at Time of BMT in 10 Patients With CHS**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age at BMT (mos)</th>
<th>Clinical Status of AP</th>
<th>Hb (g/100 mL)</th>
<th>Platelets/μL</th>
<th>ANC/μL</th>
<th>Conditioning regimen</th>
<th>HLA Compatibility/Donor (MLR)</th>
<th>GVHD Prophylaxis</th>
<th>Mononucleated Cells/kg</th>
<th>T-Cell Depletion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>1st BMT</td>
<td>12.6</td>
<td>375,000</td>
<td>2,500</td>
<td>Endoxan, 200 mg/kg</td>
<td>Identical/sister (-)</td>
<td>MTX</td>
<td>3.5 x 10^6</td>
<td>N</td>
</tr>
<tr>
<td>2</td>
<td>11</td>
<td>1st BMT</td>
<td>12</td>
<td>300,000</td>
<td>2,000</td>
<td>TBI, Cy; Endoxan, 100 mg/kg</td>
<td>Identical/sister (-)</td>
<td>MTX</td>
<td>1.7 x 10^6</td>
<td>N</td>
</tr>
<tr>
<td>3</td>
<td>11</td>
<td>2nd BMT</td>
<td>11</td>
<td>100,000</td>
<td>900</td>
<td>VP-16, 900 mg/m^2; busulfan, 16 mg/kg; Endoxan, 200 mg/kg</td>
<td>Identical/brother (-)</td>
<td>Cy</td>
<td>1.3 x 10^6</td>
<td>Y (rosetting)</td>
</tr>
<tr>
<td>4</td>
<td>11</td>
<td>2nd BMT</td>
<td>12</td>
<td>246,000</td>
<td>350</td>
<td>VP-16, 900 mg/m^2; busulfan, 16 mg/kg; Endoxan, 200 mg/kg</td>
<td>Identical/brother (-)</td>
<td>Cy</td>
<td>1.9 x 10^6</td>
<td>N</td>
</tr>
<tr>
<td>5</td>
<td>12</td>
<td>2nd BMT</td>
<td>10</td>
<td>237,000</td>
<td>360</td>
<td>VP-16, 900 mg/m^2; busulfan, 16 mg/kg; Endoxan, 200 mg/kg</td>
<td>Identical/mother (-)</td>
<td>Cy</td>
<td>1 x 10^6</td>
<td>N</td>
</tr>
<tr>
<td>6</td>
<td>12</td>
<td>2nd BMT</td>
<td>8</td>
<td>30,000</td>
<td>230</td>
<td>VP-16, 900 mg/m^2; busulfan, 16 mg/kg; Endoxan, 200 mg/kg</td>
<td>Identical/sister (-)</td>
<td>Cy</td>
<td>5 x 10^6</td>
<td>N</td>
</tr>
<tr>
<td>7</td>
<td>3</td>
<td>1st BMT</td>
<td>9.6</td>
<td>344,000</td>
<td>1,100</td>
<td>VP-16, 400 mg/m^2; busulfan, 20 mg/kg; Endoxan, 200 mg/kg</td>
<td>Identical/father (-)</td>
<td>Cy and MTX</td>
<td>1.8 x 10^6</td>
<td>N</td>
</tr>
<tr>
<td>8</td>
<td>12</td>
<td>2nd BMT</td>
<td>9.7</td>
<td>120,000</td>
<td>700</td>
<td>VP-16, 400 mg/m^2; busulfan, 26 mg/kg; Endoxan, 200 mg/kg; ATG</td>
<td>Identical/father (-)</td>
<td>Cy and MTX</td>
<td>1.9 x 10^6</td>
<td>N</td>
</tr>
<tr>
<td>9</td>
<td>12</td>
<td>2nd BMT</td>
<td>9</td>
<td>148,000</td>
<td>3,500</td>
<td>VP-16, 900 mg/m^2; busulfan, 16 mg/kg; Endoxan, 200 mg/kg; anti-LFA-1 and anti-CD2</td>
<td>1 agA/mismatched brother (+)</td>
<td>Cy</td>
<td>0.4 x 10^6</td>
<td>Y (rosetting)</td>
</tr>
<tr>
<td>10</td>
<td>11.5</td>
<td>3rd BMT</td>
<td>11.5</td>
<td>237,000</td>
<td>1,100</td>
<td>VP-16, 900 mg/m^2; Aracytine, 2 g/kg; busulfan, 16 mg/kg; Endoxan, 200 mg/kg</td>
<td>1 haplotype/mother (+)</td>
<td>Cy</td>
<td>0.3 x 10^6</td>
<td>Y (rosetting)</td>
</tr>
</tbody>
</table>

Cy was given as IV injection 3 mg/kg/d from day −1 to day 60, then orally 3 mg/kg/d from day 60 to day 180. MTX was given as IV injection: 10 mg/m^2 on days +1, 3, 6, and 11. Mouse monoclonal antibodies anti-LFA-1 and anti-CD2 were given by IV route from day −3 to day +10 (0.2 mg/kg/d).

Abbreviations: AP, accelerated phase; MLR, mixed lymphocyte reactivity; ag, antigen; MTX, methotrexate; Endoxan; Cy, cyclosporine; TBI, total body irradiation.
infections were infrequent. Cytomegalovirus (CMV) infection occurred in patients 2, 3, and 7, but was controlled by specific therapy. Herpes simplex virus (HSV) and varicella (VZV) infections also occurred in two patients (HSV in patients 1 and 3, VZV in patients 1 and 7), both of whom recovered within 12 months after BMT. Six of the matched patients are alive and well 1.5 to 12 years after BMT (Table 3). No case of hepatic complication including venoocclusive disease was detected.

**HLA-nonidentical BMT.** Engraftment of HLA-nonidentical T-cell-depleted marrow was achieved in only one of the three patients (patient 8). This patient was successfully treated for CMV infection and is alive and well 3 years after BMT. The other two patients died early after BMT from a recurrence of the accelerated phase and CMV pneumonia, respectively.

**Chimerism and Disease Correction**

Among the seven long-term survivors, three (patients 1, 5, and 6) exhibit full donor leukocyte chimerism, while the other four have sustained mixed chimerism, with a majority (patients 2 and 3) or a minority (patients 4 and 8) of donor-derived cells (Table 3). Split chimerism occurred in patient 4, in whom only host-type erythrocytes are detectable. The small proportion of donor-derived leukocytes in patients 4 and 8 has remained stable for 3 and 8 years, respectively (Table 3). No new accelerated phases have occurred in these seven patients, and significant NK cell activity was present in all seven patients (Table 4). Patient 4 has persistent mild neutropenia (1,200/µL) and occasional bacterial infections. Peripheral blood T- and B-cell populations are normal in all seven patients, with normal T- and B-cell antigen-specific responses in all but patient 8, who still requires monthly IV Ig substitution 36 months after BMT. Patient 1 has mild psychologic sequelae, while the remainder show normal psychologic sequelae.

**Table 3. Engraftment and Complications After BMT in 10 Patients With CHS**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age at BMT (mos)</th>
<th>HLA Compatibility/Donor (MLR)</th>
<th>Day of ANC &gt;500/µL</th>
<th>Day of Last Platelet Transfusion</th>
<th>Acute GVHD</th>
<th>Chronic GVHD</th>
<th>Infections (time post-BMT)</th>
<th>Abnormal Granulations (%)</th>
<th>Other Engraftment Markers</th>
<th>Relapse of AP</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>36</td>
<td>Identical/sister (-)</td>
<td>18</td>
<td>30</td>
<td>N</td>
<td>Varicella (d 12) PN, 80</td>
<td>—</td>
<td>—</td>
<td>Y, d 45</td>
<td>AxW, 13 y</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>52</td>
<td>Identical/sister (-)</td>
<td>28</td>
<td>23</td>
<td>Grade I N</td>
<td>Herpes (d 42) PN, 0</td>
<td>—</td>
<td>Not informative</td>
<td>N</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>33</td>
<td>Identical/brother (-)</td>
<td>18</td>
<td>17</td>
<td>N</td>
<td>CMV (2 mo) PN, 20</td>
<td>—</td>
<td>Red cells: 90% donor type</td>
<td>N</td>
<td>AxW, 9 y</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>28</td>
<td>Identical/brother (-)</td>
<td>25</td>
<td>13</td>
<td>Grade II N</td>
<td>CMV (1 mo) Herpes (14 mo) PN, 7</td>
<td>—</td>
<td>Red cells: 0% donor type; microsatellites: PN, 0% donor type; PBMC, 10% donor type</td>
<td>N</td>
<td>AxW, 8 y</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>4</td>
<td>Identical/mother (-)</td>
<td>19</td>
<td>15</td>
<td>Grade I N</td>
<td>CMV (5 mo) Varicella (9 mo) PN, 100</td>
<td>—</td>
<td>—</td>
<td>Y</td>
<td>Died 2 y after 2nd BMT</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>42</td>
<td>Identical/sister (-)</td>
<td>31</td>
<td>23</td>
<td>Grade I N</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>N</td>
<td>AxW, 1.5 y</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>6</td>
<td>Identical/father (—)</td>
<td>Never</td>
<td>Never</td>
<td>N</td>
<td>—</td>
<td>CMV (5 mo) Varicella (9 mo) PN, 100</td>
<td>—</td>
<td>—</td>
<td>Y</td>
<td>Died 2 y after 2nd BMT</td>
</tr>
<tr>
<td>8</td>
<td>1</td>
<td>1 ag A/ mismatched brother (+)</td>
<td>19</td>
<td>50</td>
<td>N</td>
<td>CMV (5 mo) PN, 96</td>
<td>—</td>
<td>—</td>
<td>N</td>
<td>AxW, 3 y; Ig substitution</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>33</td>
<td>1 haplotype/mother (+)</td>
<td>Never</td>
<td>Never</td>
<td>N</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Y</td>
<td>Early release; died of AP d 45</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>34</td>
<td>1 ag DR/ mismatched (+)</td>
<td>19</td>
<td>45</td>
<td>N</td>
<td>CMV</td>
<td>—</td>
<td>—</td>
<td>N</td>
<td>Died at 80; CMV pneumonia</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: NT, not tested; AxW, alive and well; PN, polymorphonuclear neutrophils; L, lymphocytes; PBMC, peripheral blood mononuclear cells.

**Table 4. NK Cell Activity in 10 Patients With CHS Before and After BMT**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Pre-BMT (%)</th>
<th>Post-BMT (%)</th>
<th>Time Post-BMT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7</td>
<td>34</td>
<td>4.5 yrs</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>36</td>
<td>9 yrs</td>
</tr>
<tr>
<td>3</td>
<td>&lt;1</td>
<td>26</td>
<td>1 yr</td>
</tr>
<tr>
<td>4</td>
<td>&lt;1</td>
<td>22</td>
<td>3 yrs</td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td>22</td>
<td>1 yr</td>
</tr>
<tr>
<td>6</td>
<td>4</td>
<td>32</td>
<td>9 mos</td>
</tr>
<tr>
<td>7</td>
<td>5</td>
<td>ND</td>
<td>—</td>
</tr>
<tr>
<td>8</td>
<td>9</td>
<td>33</td>
<td>7 mos</td>
</tr>
<tr>
<td>9</td>
<td>5</td>
<td>ND</td>
<td>—</td>
</tr>
<tr>
<td>10</td>
<td>&lt;1</td>
<td>ND</td>
<td>—</td>
</tr>
</tbody>
</table>

NK cell activity was measured in a standard chromium release assay using K562 cells. Results are given for an effector:target ratio of 50:1. Normal value was >15%.

Abbreviation: ND, not determined.
growth and development, with normal school attendance. There were no neurologic sequelae. Hair, eye, and skin albino-

nism were not altered by BMT.

DISCUSSION

Allogeneic BMT was effective in treating the hematologic manifestations of CHS in six of seven recipients of HLA-

identical marrow and one of three recipients of HLA-non-

identical marrow. This confirms and extends previous reports of BMT efficacy in CHS and in the beige mouse model. In the absence of BMT, CHS is usually fatal before the age of 10 years, although a few patients survive for more than 20 years. No patients with accelerated phases have sur-

vived in the absence of BMT.13

No accelerated phases have occurred during the several years of follow-up after BMT, even in patients who had limited donor-type leukocyte engraftment. This is reminis-

cent of patients successfully treated by means of BMT for familial hemophagocytic lymphohistiocytosis (FHL), in whom no FHL relapse occurred despite the presence of only a small proportion of donor-derived leukocytes. As the manifestations of FHL are very similar to those of the accel-

erated phase of CHS, it appears that a minority of normal leukocytes are sufficient to contain abnormally activated lymphocytes and macrophages in FHL and the accelerated phase of CHS, including within the CNS. Whether donor-

derived NK cells or other donor-derived cytotoxic leukocytes participate in the control of lymphocyte and macrophage activation remains to be determined.

Our findings indicate that aggressive BMT conditioning is not necessary, thus avoiding the risk of significant long-
term sequelae. It should, however, be noted that the condition ing regimen we used did not abrogate host hematopoiesis in one patient, for reasons that are unclear. The lack of engraftment of HLA-nonidentical marrow in two of three such patients illustrates the ability of the immune system—though deficient in NK cell activity—to induce primary graft failure in CHS. As a result, although BMT with an HLA-identical sibling or parent can be regarded as the treat-

ment of choice in CHS, especially for patients in remission from an accelerated phase, HLA-nonidentical BMT is still an experimental procedure in this setting. The alternative of matched unrelated donor transplant can be proposed as a valuable option in the absence of a family-matched do-

nor.24,25

Although no extrahematopoietic manifestations of CHS have occurred in the seven long-term survivors of BMT, the occurrence of mild manifestations such as peripheral or central neuropathy cannot be ruled out. Indeed, extrapiramidal manifestations have been recently reported to occur in the late-onset mild form of CHS. It is unclear whether these manifestations are caused by a disease-related neurologic involvement or as CNS localization of accelerated phase.

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Treatment of Chediak-Higashi syndrome by allogenic bone marrow transplantation: report of 10 cases

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