Fanconi’s Anemia Treated by Allogeneic Marrow Transplantation


Eight patients with Fanconi’s anemia were given cyclophosphamide alone (seven patients) or combined with procarbazine and antithymocyte globulin (one patient) followed by marrow grafts from HLA-identical siblings. All patients had engraftment. Seven developed acute and three chronic graft-versus-host disease (GVHD). Three patients died with GVHD and infectious complications (days 19, 56, and 82) and one with an intracerebral hemorrhage (day 540). Four patients are surviving 647–3435 days after grafting, two are well, and two have chronic GVHD that is improving. These results show that Fanconi’s anemia can be treated successfully by allogeneic marrow transplantation.

FANCONI’S ANEMIA is an autosomal recessive disorder associated in about half of the cases with congenital anomalies. These include central nervous system malformations with mental retardation, abnormalities of skeleton, heart, and kidneys, hypogonitalism, abnormal skin pigmentation, and splenic atrophy.1-4 Almost all patients have abnormal chromosomes with multiple breaks and gaps in hemopoietic cells and tissue fibroblasts.5 The course of the disease is characterized by progression of pancytopenia and marrow aplasia, resulting in the death of most patients due to hemorrhage or infections. There is also an increased incidence of acute myelocytic leukemia and other tumors.6

Since aplastic anemia of other etiologies can be treated successfully by allogeneic marrow transplantation,7 it appeared appropriate to apply this treatment also to patients with Fanconi’s anemia. Several transplant teams have reported their results in small numbers of patients with Fanconi’s anemia.8-10 We summarize here our experience in eight patients.

MATERIALS AND METHODS

Table 1 shows some patient characteristics. The patients’ hematocrits were 15%-27% (median 21%), reticulocyte counts 0.2%-2.1% (median 0.9%), granulocyte counts 0.15-1.1 (median 0.5) x 10^9/liter, and platelet counts 1.3-17 (median 9.5) x 10^9/liter. The marrow cellularity was <5%-30% (median 5%) with erythroid precursors being 0%-100% (median <5%), myeloid precursors <1%-20% (median <5%), and megakaryocytes 0%-10% (median <5%) of normal. Patients 4 and 5 were untransfused; the remaining patients had received 2 to >50 (median 28) units of red blood cells and 10 to >50 (median 37) units of platelets before transplantation. Chromosomal abnormalities in phytohemagglutinin-stimulated (72-90 hr) peripheral blood lymphocytes and in marrow cells were found in 13%-63% (median 34%) of the metaphase spreads (25-135/patient) examined. Quadriradial configurations were found in all except patient 7. The marrow donors were always HLA-identical siblings. They were 3-32 yr old (median 13.5). In 4 transplants the donors were of the same sex (2 male, 2 female) and in 4 of the opposite sex (2 female & male, 2 male & female). ABO blood group incompatibility was present in 4 patients: 3 minor (0 → A/B) and 1 major (A → 0). The immunosuppressive regimens used in preparation for transplantation and the marrow doses infused are given in Table 1. Patient 6 was also given unirradiated donor buffy coat cells for 5 days after grafting.15 All patients were given intermittent doses of methotrexate as prophylaxis for graft-versus-host disease (GVHD) after grafting.19 Methods of assessing engraftment by determination of red cell antigens and isoenzymes and karyotype analysis,18,19 criteria for the diagnosis of acute and chronic GVHD, a grading system, and therapeutic manipulations have been described before.19,20

The marrow transplant protocols and consent forms for these studies were approved by the Human Subjects Review Committee of the Fred Hutchinson Cancer Research Center or of the University of Washington School of Medicine.

RESULTS

The results are summarized in Table 1.

Survival

Four of the 8 patients are surviving 647–3435 days after transplantation. Four patients died 19, 56, 82, and 540 days after transplantation.

Engraftment

All eight patients had engraftment, as indicated by rising blood cell counts. Marrow and peripheral blood cells obtained after grafting were of donor origin, as documented by normal donor karyotype on cytogenetic analysis (seven patients), donor red cell enzyme and antigen phenotypes (four patients), and donor ABO blood groups (three patients). Patient 4 had evidence of engraftment but required two additional infusions of marrow from the same donor (days 35, 391) since he
### Table 1. Data on 8 Patients With Fanconi’s Anemia Given Marrow Grafts From HLA-Identical Sibling Donors

| Patient No. (UPN)* | Age (yr/Sex) | Other Disease Manifestations | Duration of Aplastic Anemia (mo) | Previous Treatment | Date of Transplant | Conditioning Regimen | Marrow Cell Dose \((x \times 10^6/kg)\) | Last Dose of MTX* \((Day)\) | Complications | Acute Severity (Day of Onset) | Organs Involved | Chronic Extent | Outcome Performance Score† |
|-------------------|--------------|-----------------------------|----------------------------------|---------------------|-------------------|---------------------|----------------------|-----------------|-------------------|----------------|----------------|--------------------------|
| 1 (302)           | 6/F          | Small stature               | 24                               | Prednisone, Cyclophosphamide, Azathioprine | 3/7/73            | CY 50 mg/kg × 4     | 11.2                 | 102             | M, HC, intrahepatic hemorrhage | I (48) | Skin      | No                       | Alive >3435 days (100%) Small stature, adolescent scoliosis, absence of secondary sex characteristics |
| 2 (317)           | 8/M          | Small stature               | 48                               | Dexamethasone, Omnomethione, Nandrolone | 12/5/73           | CY 50 mg/kg × 3     | 6.7                  | 11              | M, HC, cardiac arrhythmias, sepsis (E. coli) | III (5) | Skin, liver, intestine | NA                       | Died day 19 Gram-negative sepsis, GVHD |
| 3 (398)           | 4/F          | Short stature               | 8                                | Omnomethione, Prednisone, Procarbazine, Antithymocyte globulin | 5/6/74            | CY 50 mg/kg × 4     | 6.5                  | 42              | M, HC, herpes zoster, sepsis (S. aureus, C. albicans, multiple gram-negative organisms) | III (11) | Skin, liver, intestine | NA                       | Died day 82 Gram-negative sepsis, GVHD |
| 4 (717)           | 12/M         | Cafe-au-lait spots          | 1                                | Dexamethasone       | 7/22/77           | CY 50 mg/kg × 4     | 2.5                  | 54              | M, graft failure, herpes zoster, septic necrosis of tibial epiphyses, intracerebral hemorrhage | I (46) | Skin      | Yes — Skin Mucosa, Sicca syndrome, Liver | Died day 540 Thrombocytopenia, CNS hemorrhage |

(continued)
Table 1. Data on 8 Patients With Fanconi’s Anemia Given Marrow Grafts From HLA-Identical Sibling Donors (Cont’d.)

<table>
<thead>
<tr>
<th>Patient No. (UPN)*</th>
<th>Age (yr)/Sex</th>
<th>Other Disease Manifestations</th>
<th>Duration of Aplastic Anemia (mo)</th>
<th>Previous Treatment</th>
<th>Date of Transplant</th>
<th>Conditioning Regimen</th>
<th>Marrow Cell Dose (x 10^6/kg) (Day)</th>
<th>Last Dose of MTX* (Day)</th>
<th>Complications</th>
<th>Severity (Day of Onset)</th>
<th>Organs Involved</th>
<th>Chronic (Extent)</th>
<th>Outcome (Performance Score)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 (821)</td>
<td>5/M</td>
<td>Short stature, Microcephaly, Low-set ears, Retarded bone age, Cafe-au-lait spots</td>
<td>6</td>
<td>Prednisone, Nandrolone</td>
<td>4/5/78</td>
<td>CY 50 mg/kg x 4</td>
<td>4.2</td>
<td>47</td>
<td>M, HC, septicemia (E. coli), pneumonia (E. coli)</td>
<td>III (3)</td>
<td>Skin, liver, intestine</td>
<td>NA</td>
<td>Died day 56</td>
</tr>
<tr>
<td>6 (927)</td>
<td>20/F</td>
<td>Short stature, Pigmentation</td>
<td>65</td>
<td>Prednisone, Oxymetholone, Fluoxymesterone, Pyridoxine</td>
<td>12/7/78</td>
<td>CY 50 mg/kg x 4</td>
<td>5.9</td>
<td>102</td>
<td>M, herpes simplex (disseminated), myoclonic seizures, aspergillus, neurogenic of humoral heads</td>
<td>I (53)</td>
<td>Skin</td>
<td>Yes—Skin, mucosa, vagina, esophagus, conjunctiva, liver, myocardial, arthralgia</td>
<td>Alive &gt;1334 (85%)</td>
</tr>
<tr>
<td>7 (983)</td>
<td>14/F</td>
<td>Short stature, Cafe-au-lait spots</td>
<td>62</td>
<td>Prednisone, Oxymetholone, Iron</td>
<td>4/19/79</td>
<td>CY 50 mg/kg x 4</td>
<td>4.8</td>
<td>96</td>
<td>M, HC, congestive heart failure, pannusitis</td>
<td>0</td>
<td>No</td>
<td>Alive &gt;1201 (100%)</td>
<td>Absence of secondary sex characteristics</td>
</tr>
<tr>
<td>8 (1286)</td>
<td>9/M</td>
<td>Short stature, Pigmentation, Syndactyly</td>
<td>60</td>
<td>Prednisone, Oxymetholone</td>
<td>10/24/80</td>
<td>CY 50 mg/kg x 4</td>
<td>3.3</td>
<td>6</td>
<td>M, HC, intrahepatic hemorrhage</td>
<td>III (8)</td>
<td>Skin, liver, intestine</td>
<td>Yes—Skin, Liver</td>
<td>Alive &gt;647 (100%)</td>
</tr>
</tbody>
</table>

*Abbreviations: UPN, unique patient number; MTX, methotrexate; GVHD, graft-versus-host disease; CY, cyclophosphamide; ATG, horse antithymocyte globulin; CNS, central nervous system; NA, not applicable; M, mucositis; HC, hemorrhagic cystitis.
†Survival as of 8/1/82.
‡Had poor graft function presumably due to impaired proliferative potential of donor marrow. No lymphohemopoietic cells of host type could be detected after transplantation.
never achieved normal counts. In vitro cultures of the donor's marrow revealed poor growth of granulocytic precursors (CFU-C). In addition, 27% of the metaphase spreads of the donor's phytohemagglutinin-stimulated peripheral blood lymphocytes showed chromosomal abnormalities, including quadriradial configurations. This suggests that graft failure in this patient may have been due to impaired proliferative ability of the donor's marrow. The patient died eventually from an intracerebral hemorrhage. Patient 5 had good engraftment and developed severe GVHD. Although he died with severe neutropenia, this appeared to be related to a gram-negative septicemia rather than rejection. All surviving patients have normal hematologic parameters.

GVHD

Seven of 8 patients developed acute GVHD with onset on days 3–53. This was mild and transient in case 1, but severe in 4 patients, and of these (patients 2, 3, 5) died with GVHD and associated complications. Patient 8 progressed to mild chronic GVHD, which is resolving; his performance score is 100%. Patients 4 and 6 had mild acute GVHD progressing to chronic GVHD. Patient 6, who is surviving, has improved to a performance score of 85%. Patient 7 never had evidence of GVHD.

Miscellaneous Problems

Severe mucositis was present in all patients and six developed hemorrhagic cystitis. Two patients had an intrahepatic hemorrhage manifested by acute onset of pain in the right upper abdomen and documented by angiography and computerized tomography. Both of these patients recovered. Two patients had evidence of peliosis or adenoma hepatitis, which have regressed to normal after transplantation.

DISCUSSION

The present study shows that allogeneic marrow grafts can be carried out successfully in patients with Fanconi's anemia. Five of 8 patients survived more than 1 yr and 4 are alive 1.5–9 yr after grafting. It is of interest that the patient who died after 1 yr had received his graft from a donor with chromosomal abnormalities similar to those found in the patient. This donor's cells also showed abnormal growth of CFU-C in vitro. It is possible that the donor has latent Fanconi's anemia and that the poorly functioning graft was the result of a defect in the donor's marrow cells. Survival in this small group of patients

Table 2. Data on Patients With Fanconi's Anemia Treated by Marrow Transplantation at Other Centers

<table>
<thead>
<tr>
<th>Reference</th>
<th>No.</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Conditioning Regimen*</th>
<th>Marrow Cell Dose (× 10^6/kg)</th>
<th>Acute GVHD</th>
<th>Chronic GVHD</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Druce 7</td>
<td>1</td>
<td>10</td>
<td>M</td>
<td>CY 50 mg/kg x 4</td>
<td>2.0</td>
<td>Yes</td>
<td>No</td>
<td>Alive 11 mo</td>
</tr>
<tr>
<td>Barrett 11</td>
<td>1</td>
<td>14</td>
<td>M</td>
<td>CY 50 mg/kg x 4</td>
<td>6.0</td>
<td>No</td>
<td>No</td>
<td>Alive &gt;4.5 yr</td>
</tr>
<tr>
<td>Kersey 16</td>
<td>1</td>
<td>12</td>
<td>M</td>
<td>CY 50 mg/kg x 4</td>
<td>13.7</td>
<td>Yes</td>
<td>Yes</td>
<td>Died day 35; GVHD</td>
</tr>
<tr>
<td>Gluckman 13</td>
<td>5</td>
<td>7</td>
<td>F</td>
<td>CY 50 mg/kg x 4</td>
<td>4.5</td>
<td>Yes</td>
<td>No</td>
<td>Alive &gt;3 yr</td>
</tr>
<tr>
<td>Patient 11</td>
<td>5</td>
<td>11</td>
<td>M</td>
<td>CY 50 mg/kg x 4</td>
<td>2.0</td>
<td>Yes</td>
<td>Yes</td>
<td>Died day 42; GVHD</td>
</tr>
<tr>
<td>Gluckman 19</td>
<td>10</td>
<td>10</td>
<td>F</td>
<td>CY 50 mg/kg x 3</td>
<td>1.8</td>
<td>Yes</td>
<td>Yes</td>
<td>Died day 150; hepatic necrosis</td>
</tr>
<tr>
<td>Ramsey 17</td>
<td>1</td>
<td>13</td>
<td>M</td>
<td>CY 50 mg/kg x 4</td>
<td>7.6</td>
<td>Yes</td>
<td>Yes</td>
<td>Died day 20; GVHD</td>
</tr>
<tr>
<td>Borton 14</td>
<td>2</td>
<td>9</td>
<td>F</td>
<td>CY 50 mg/kg x 4</td>
<td>4.8</td>
<td>Yes</td>
<td>Yes</td>
<td>Died day 6; GVHD</td>
</tr>
<tr>
<td>Patient 8</td>
<td>8</td>
<td>8</td>
<td>M</td>
<td>CY 250 mg/kg over 4 days</td>
<td>4.6</td>
<td>Yes</td>
<td>Yes</td>
<td>Died at 2.8 mo; GVHD; interstitial pneumonia (Herpes simplex virus)</td>
</tr>
<tr>
<td>Holk 18</td>
<td>1</td>
<td>12</td>
<td>F</td>
<td>CY 50 mg/kg x 4</td>
<td>1.5</td>
<td>No</td>
<td>No</td>
<td>Alive &gt;4.5 yr</td>
</tr>
</tbody>
</table>

*Abbreviations as in Table 1. TLI, total lymphoid irradiation. 6MP, 6-mercaptopurine.
†GVHD, graft-versus-host disease; eight patients were not at risk for chronic GVHD.
‡These patients were given maternal marrow grafts and received donor buffy coat cells following the marrow infusion.
§Dose not given.
‖The Registry requests the following statement: "The data presented were obtained from the Statistical Center of the International Bone Marrow Transplant Registry. The analysis has not been reviewed or approved by the Advisory Committee of the Registry."
with Fanconi’s anemia was similar to that in patients transplanted for aplastic anemia of other etiologies. 7–10,14,16,18,21,25

However, the present study confirmed the impression of other investigators 13 that patients with Fanconi’s anemia have a more difficult postgrafting course. There was a high incidence of hemorrhagic cystitis and severe mucositis. In vitro studies indicate that cells from patients with Fanconi’s anemia are unusually sensitive to various antimetabolites and alkylating agents, including cyclophosphamide. 26 Gluckman et al. speculate that patients with Fanconi’s anemia may show a similar sensitivity to cyclophosphamide in vivo as these cells do in vitro. 13,26 This hypothesis might help to explain such frequent complications as severe mucositis and cystitis.

The incidence of moderately severe to severe GVHD (four of eight patients) is probably not significantly different from the overall incidence of 35% in other patients. 16,19 However, the patients in the present study were in an age group (median 8.5 yr) in which the incidence of GVHD is usually lower. 22 Furthermore, in patients with Fanconi’s anemia, GVHD appeared as early as day 3 and was associated with many complications, an observation also made by others. 13 Nevertheless, four patients are surviving and two are free of GVHD. These results compare favorably with those reported by others (Table 2). In contrast to our study, however, two of the patients reported by Gluckman et al. 13 received transplants from donors other than HLA genotypically identical siblings. Furthermore, the majority of these patients apparently had rather severe nonhematologic manifestations of the disease. This in turn may correlate with more profoundly impaired repair mechanisms of host cells resulting in severe manifestations of GVHD.

Without transplantation, the outlook of patients with Fanconi’s anemia is poor due to the risk of fatal hemorrhage or the development of acute myelogenous leukemia. 5 Furthermore, treatment with androgens has significant side effects, in particular, hepatotoxicity. 28 Therefore, the earlier poor results with marrow transplantation in patients with Fanconi’s anemia should not deter new attempts at applying this treatment to additional patients. Experience, refined techniques, modified conditioning regimens, 29 and better support promise improved results.

ACKNOWLEDGMENT

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