Selection of Patients for Bone Marrow Transplantation in Severe Aplastic Anemia

By Bruce M. Camitta, Joel M. Rappeport, Robertson Parkmon, and David G. Nathan

Despite androgens and intensive supportive care, satisfactory survival in severe aplastic anemia remains at 20% or less. Histocompatible bone marrow transplantation can restore normal hematopoiesis in approximately 40% of similarly severe individuals. Delay of transplantation for 3 wk after diagnosis allows time for proper evaluation and for many spontaneous recoveries. Further delay increases risks of fatal complications and decreases chances for successful transplantation while the incidence of spontaneous remission declines. When available, early histocompatible bone marrow transplantation may be the treatment of choice for severe aplastic anemia.

Survival curves that define the course of patients with aplastic anemia are biphasic. An initial steep descent is followed after 6–12 mo by a more gradual decline. This observation is probably explained by the existence of two broad categories of patients who have either severe or moderate disease. Advances in supportive care (antibiotics, transfusions, and hormones) have probably contributed to an improved outlook for groups of moderately affected patients in which long-term survivals of 50% are now quite common in contrast to 20% (or less) prior to 1950. There is evidence that androgen therapy may also have contributed to this decreased mortality in such patients.

In contrast to the course of mildly affected patients, long-term survival of patients with severe aplastic anemia has remained poor (approximately 15%). Even institutions reporting 50% recovery overall have had little success in the treatment of severe disease. These patients are probably responsible for the sharp descent portion of the over-all survival curve, since more than half die within 3–6 mo of diagnosis. Neither androgens nor other advances in supportive care appear to have significantly altered mortality, although the potential value of maximal environmental asepsis and better transfusion techniques have not yet been thoroughly investigated in this group. Clearly, any effort to improve survival in aplastic anemia overall must focus on individuals with severe disease.

Marrow transplantation offers a major new tool in therapy of severe aplastic...
anemia. However, the technique is fraught with hazard and should not be applied in patients who would recover with conservative management. In this paper, we present our experience with 26 patients with aplastic anemia treated by or reported to us during the past 2 yr. In order to define our capacity to recommend a marrow transplant appropriately, each patient was prospectively assigned to a group designated mild to moderate or severe. Histocompatibility testing was performed on immediate family members of all severe patients. If a suitable donor was available, marrow transplantation was recommended for severe patients without regard to length of prior conservative treatment.

Three subsets of aplastic anemia patients were then followed: those with mild to moderate disease treated conservatively, those with severe disease treated conservatively (androgens, corticosteroids, transfusions, antibiotics), and those with severe disease treated with marrow transplantation. Our results indicate that patients initially classified as mild to moderate often become severe. Survival on conservative therapy of individuals initially classified as severe or changed from mild to severe is poor. Marrow transplantation may offer an enhanced opportunity for marrow reconstitution and survival in severely affected patients.

MATERIALS AND METHODS

All patients with acquired aplastic anemia who were treated or consulted on by the Children's Hospital Medical Center or the Peter Bent Brigham Hospital between January 1972 and December 1973 form the basis of this report. Most of the patients were referred for possible marrow transplantation. No patients were aplastic secondary to chemotherapy or radiotherapy for malignancies. Three had taken medication which might have caused aplasia. Screening tests to detect underlying diseases included BUN, liver functions, sugar water hemolysis, chromosomes, skeletal films, marrow scans with $^{111}$In, hemoglobin and serum electrophoresis. Wherever possible, marrow biopsies were done in addition to aspirates. Clinical classification of the patients was performed by means of arbitrary criteria. Patients considered to have mild to moderate disease had pancytopenia (hematocrit < 38%, PMN < 2500/cu mm, platelets < 120,000/cu mm) and variably decreased marrow cellularity. Patients considered to have severe aplastic anemia had marked pancytopenia (at least two of the following were present: PMN < 500/cu mm, platelets < 20,000/cu mm, corrected reticulocyte count < 1%) and marked marrow hypocellularity, with more than 65% of residual marrow cells being nonhematopoietic.

Transplantation Procedures

Details of histocompatible donor selection, marrow procurement, isolation techniques, and immunosuppression have been previously reported. Pretransplant immunosuppression was accomplished with cyclophosphamide. If presensitization to donor cells was present (as evidenced by previous marrow graft rejection, cytotoxic antibodies, or cell-mediated immune lysis against donor tissue), rabbit antihuman-thymocyte serum (ATS, 0.1-0.3 cc/kg on days -6, -4, -2) and procarbazine (12.5 mg/kg orally on days -7, -5, -3) were given in addition to cyclophosphamide. In one case, 1000 rads total body irradiation (TBR) replaced cyclophosphamide.

Nontransplant Patients

Patients without histocompatible donors received maximum support (including androgens). In several, but not all, cases this included isolation procedures identical to those used for transplant patients.

Informed Consent

A complex mechanism was arranged to insure informed donor, recipient, and family consent. Details of this procedure are given elsewhere.
RESULTS

Twenty-eight patients with aplastic anemia were observed during the 2-yr period of this study. Twelve were evaluated here initially, while sixteen were referred by other physicians. Two patients (one with mild, the other with severe aplasia) achieved hematologic recovery within 2 wk of onset of androgen and/or corticosteroid therapy but developed acute lymphocytic leukemia 2 mo later. They are assumed to have had leukemia as the cause of their aplastic anemia and are not included in the subsequent analyses. Data on the remaining 26 cases are summarized in Table 1.

Patients with severe aplastic anemia were transplanted or followed conservatively. Eighteen patients with severe disease did not receive transplants. Reasons included lack of a histocompatible donor (ten), rapid onset of hematologic improvement (three), early death (one), refusal to undergo transplant (one), and referring physician’s desire to observe the patient longer (three). No patient was denied transplantation because of poor physical condition. Both transplant and nontransplant patients were hemorrhagic, and only one had not been multiply transfused. In addition, most individuals had (or previously had) serious infections. Thus transplant and nontransplant groups were comparable clinically and hematologically at the time of treatment selection (Table 1).

As indicated above, the course of a third group of patients, who were initially classified as mild to moderate, was also followed. However, only seven patients were initially mild to moderate, and all became severe. In addition, when initially mild patients converted to severe their clinical characteristics were identical to the initially severe patients (except for the additional survival attributable to the time that they were only mildly to moderately ill). Therefore, initially mild to moderate patients are included with the initially severe patients for the purpose of this report.

Table 1. Characteristics of Patients With Severe Aplastic Anemia at Time of Transplant Decision

<table>
<thead>
<tr>
<th></th>
<th>Nontransplanted</th>
<th>Transplanted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>18</td>
<td>8</td>
</tr>
<tr>
<td>Age-median (range)</td>
<td>12 (4–45)</td>
<td>15 (7–42)</td>
</tr>
<tr>
<td>Male/Female</td>
<td>7/11</td>
<td>4/4</td>
</tr>
<tr>
<td>Hematologic values at onset of illness, mean (range)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PMN/cu mm</td>
<td>520 (20–1900)</td>
<td>440 (25–900)</td>
</tr>
<tr>
<td>Platelets/cu mm</td>
<td>20 × 10^3 (0–108 × 10^3)</td>
<td>20 × 10^3 (2–70)</td>
</tr>
<tr>
<td>Reticulocytes (%)*</td>
<td>0.5 (0–2.4)</td>
<td>0.5 (0.1–1.5)</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>23 (9–36)</td>
<td>25 (15–32)</td>
</tr>
<tr>
<td>Number initially mild</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Interval: Diagnosis of severe aplastic anemia to transplant decision in months, mean (range)</td>
<td>2 (0–18)</td>
<td>3 (2–7)</td>
</tr>
<tr>
<td>Hematologic values at transplant decision, mean (range)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PMN/cu mm</td>
<td>290 (0–1000)</td>
<td>150 (29–800)</td>
</tr>
<tr>
<td>Platelets/cu mm + 1000</td>
<td>6 × 10^5 (0–19)</td>
<td>6 × 10^5 (1–18)</td>
</tr>
<tr>
<td>Reticulocytes (%)*</td>
<td>0.4 (0–1.3)</td>
<td>0.3 (0–0.9)</td>
</tr>
</tbody>
</table>

*Corrected for hematocrit.
Table 2. Outcome of Patients With Severe Aplastic Anemia

<table>
<thead>
<tr>
<th>Nontransplanted (18)</th>
<th>Transplanted (8)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Early responders</strong></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Alive with engraftment &gt;6 mo</td>
</tr>
<tr>
<td>2 complete remission</td>
<td>3*</td>
</tr>
<tr>
<td>1 partial remission</td>
<td>Died</td>
</tr>
<tr>
<td><strong>Group comparable to transplanted patients</strong></td>
<td>12 (10 within 4 mo)</td>
</tr>
<tr>
<td>15</td>
<td>Died</td>
</tr>
<tr>
<td>Died</td>
<td>2 no improvement</td>
</tr>
<tr>
<td>Alive &gt;6 mo</td>
<td>1 partial improvement</td>
</tr>
</tbody>
</table>

*One patient died 1 yr post-transplant of persistent hepatitis, sepsis, and chronic graft-versus-host disease.†
†See Table 3 for causes.

Nontransplanted Cases

The outcome of 18 nontransplanted cases is shown in Table 2. Twelve patients died, all but two within 4 mo of diagnosis of severe aplasia. In four fatal cases, marrow donors were available, but referring physicians or families elected further androgen therapy (despite 2-5 mo without previous improvement on these agents).

Six patients (33%) are alive. However, three began recovery within 3 wk of diagnosis (Fig. 1) and thus would not have been eligible for transplantation (two of these had a strong history of drug exposure—two other patients in our series with such exposure died). Two of the three other survivors remain ill with no hematologic improvement (at 15 and 36 mo.) One improved from severe to moderate at 12 mo. Her hematologic values are now normal. Thus, of 15 nontransplanted individuals who might have been eligible for transplantation, 80% did not survive for 6 mo or more, and only one of the survivors has improved.

Transplanted Patients

Eight severely affected patients were transplanted (Tables 2 and 3). All except JO had received androgens for at least 2 mo without apparent benefit. All except JW were hemorrhagic and had been multiply transfused. MB and MF were septic and died shortly after marrow infusion despite multiple antibiotics and PMN transfusions.

Three patients had excellent courses with proven donor reconstitution of hematologic elements. None of these were septic prior to transplant. One (TD) died 1 yr later of persistent hepatitis, probable graft-versus-host disease (GvH) and sepsis.† The other two remain well. JW also showed prompt engraftment, but severe vomiting due to GvH prevented administration of oral nonabsorbable antibiotics. She succumbed to intestinal overgrowth with proteus mirabilis and resultant sepsis.

Patients JC and CC rejected their initial grafts after brief takes. Regrafting was attempted using an immunosuppressive regimen capable of overcoming presensitization in a canine model.§ CC showed no evidence of re-engraftment. JC had an excellent take but died of disseminated fungal infection and GvH.
Over-all survival in transplanted patients was similar to the entire group of nontransplanted cases. However, when early nontransplanted responders are eliminated from consideration (see above) the outlook for the transplanted patients appears to be better than the nontransplanted group.

**DISCUSSION**

Thomas et al. have restored normal hematopoietic functions for 1 yr or more in 11 of 24 severe aplastics by means of histocompatible sibling bone marrow transplants. Our results are similar albeit in a smaller group followed for a briefer time. The combined 44% survival with transplantation should be contrasted with 10%-20% 1-yr survival (often without improvement) in similarly severe cases treated without transplants.

One-third of transplant deaths are due to sepsis, one-third to graft rejection, and one-third to GVH. In our experience, pretransplant septicemia substantially increases transplant mortality. Multiple transfusions increase marrow

**Table 3. Marrow Transplantation for Aplastic Anemia**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Etiology</th>
<th>Duration (mo)</th>
<th>Age</th>
<th>Sex</th>
<th>Donor</th>
<th>Cells Infused ($\times 10^9$/kg)</th>
<th>&quot;Take&quot;</th>
<th>GVH</th>
<th>Survival (days)</th>
<th>Cause of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>M.B. ?</td>
<td>Hepatitis</td>
<td>6</td>
<td>62</td>
<td>F</td>
<td>M</td>
<td>2.3</td>
<td>Yes</td>
<td>4</td>
<td>2</td>
<td>Sepsis</td>
</tr>
<tr>
<td>T.D.</td>
<td>Chloro</td>
<td>3</td>
<td>14</td>
<td>M</td>
<td>M</td>
<td>2.3</td>
<td>Yes</td>
<td>2-3+</td>
<td>375</td>
<td>Hepatitis, sepsis</td>
</tr>
<tr>
<td>J.W.</td>
<td>Chloro</td>
<td>98</td>
<td>13</td>
<td>F</td>
<td>M</td>
<td>2.7</td>
<td>Yes</td>
<td>4</td>
<td>21</td>
<td>GVH, sepsis</td>
</tr>
<tr>
<td>C.C. ?</td>
<td>?</td>
<td>4</td>
<td>23</td>
<td>M</td>
<td>M</td>
<td>1.8</td>
<td>Yes</td>
<td>+/-</td>
<td>Graft rejected (day 24)</td>
<td></td>
</tr>
<tr>
<td>J.O. ?</td>
<td>?</td>
<td>2</td>
<td>15</td>
<td>M</td>
<td>M</td>
<td>3.0</td>
<td>Yes</td>
<td>1</td>
<td>540+</td>
<td>Sepsis</td>
</tr>
<tr>
<td>M.F. ?</td>
<td>?</td>
<td>7</td>
<td>15</td>
<td>M</td>
<td>M</td>
<td>2.9</td>
<td>No</td>
<td>5</td>
<td>75</td>
<td>Sepsis</td>
</tr>
<tr>
<td>J.C. ?</td>
<td>?</td>
<td>2</td>
<td>7</td>
<td>F</td>
<td>M</td>
<td>2.5</td>
<td>Yes</td>
<td>+/-</td>
<td>Graft rejected (Day 26)</td>
<td></td>
</tr>
<tr>
<td>S.C. ?</td>
<td>?</td>
<td>3</td>
<td>24</td>
<td>F</td>
<td>F</td>
<td>2.4</td>
<td>Yes</td>
<td>1+</td>
<td>360+</td>
<td>Sepsis</td>
</tr>
</tbody>
</table>

*ALS, procarbazine, TBR preparation.  
†ALS, procarbazine, cytoxan preparation.
rejection rates in canine systems\textsuperscript{21} by causing sensitization to transplantation antigens. This may also be true in man.\textsuperscript{22} Thus, mortality from sepsis and rejection should be significantly decreased by performing transplantation earlier in the course of aplasia. However, such early action would increase transplantation of patients who might respond to conservative care alone unless adequate prognostic indices were available.

Multiple factors have been studied for prognostic value in aplastic anemia. Most helpful have been levels of PMN and reticulocytes\textsuperscript{2,9} or percentages of nonhematopoietic cells in the bone marrow.\textsuperscript{1,11} Individuals with marked abnormalities tend to pursue a short lethal course.\textsuperscript{1,12} Mortality approaches 90\%. More than 50\% of less severely affected patients recover. However, mild patients frequently become severe and can then pursue a short lethal course as did all of the mild patients reported here. Furthermore, as exemplified by Fig. 1, none of the hematologic factors mentioned above (either alone or in combination) predict with certainty which severely affected patients will recover. Bone marrow scanning with indium or ferrokinetic studies have not been of additional prognostic help in our hands.

\begin{table}[h]
\centering
\caption{Predicted Effect of Histocompatible Transplantation on Survival of 100 Hypothetical Patients With Severe Aplastic Anemia}
\begin{tabular}{|l|c|}
\hline
\textbf{Protocol} & \textbf{Survivors} \\
\hline
Nontransplant protocol & \\
10\% early responders\textsuperscript{*} & 10 \\
10\% later responders\textsuperscript{*} & 10 \\
Total survivors & 20 \\
\hline
Early transplant protocol & \\
10\% early responders & 10 \\
Transplanted (90) assume 40\% transplant success\textsuperscript{†} & 36 \\
Total survivors & 46 \\
\hline
But of transplant patients: 4 survivors would have survived without transplant (later responders) and 6 died who would have survived without transplant (later responders) & \\
Therefore: Net gain from early transplant per se & 26 \\
\hline
4-mo delayed transplant protocol & \\
50\% pretransplant deaths\textsuperscript{‡} (50) & \\
10\% early responders & 10 \\
5\% later responders & 5 \\
Transplanted (35) assume 40\% transplant success & 14 \\
Total survivors & 29 \\
\hline
But of transplant patients: 2 survivors would have survived without transplant (later responders) and 3 died who would have survived without transplant (later responders) & \\
Therefore: Net gain from late transplant per se & 9 \\
\hline
\end{tabular}
\end{table}

These calculations are based on published survival statistics (see text).
\textsuperscript{*}The division between early and late responders is based on reference 16. Conclusions are not significantly altered if responses are all early or all late.
\textsuperscript{†}Based on this series and reference 14.
\textsuperscript{‡}Based on references 1 and 2.
All Patients
- Isolation
  - Rule out underlying disease.

Identical Twins
- Transplant at once. No immunosuppression required.

Others
- Check histocompatibility at once.
  - While waiting or No donor
    - Androgens
    - Corticosteroids
    - Transfusions
      - Limited
      - Random donors

Donor available
- Transplant—Begin three weeks after presentation.
  - Donor may be used for transfusion support if transplantation declined.

Fig. 2. Current management of newly diagnosed patients with severe aplastic anemia.

Androgens are required for maintenance of hematologic responses in a small number of aplastics. However, there is little evidence that anabolic agents increase the frequency, rate, or degree of response in large series of patients. The major action of these agents appears to be erythropoietic, and initial responses are not usually seen for 2–3 mo. Thus, reliance on androgens to produce increases of PMN and platelets in severe aplasia exposes patients to several months (at least) of risk from infection and hemorrhage. Early transplantation would decrease this period of risk.

Another approach to severe aplastic anemia is “supersupportive” care. Sterile environment regimens have significantly decreased the incidence of infections in leukemic patients. PMN transfusions may be helpful in treating established infections. If histocompatible donors are available, long-term platelet support is possible. Indeed, several patients treated by Yankee et al. recovered normal marrow function after 2–5 yr of platelet support plus antibiotics for infections. On the other hand, increased use of transfusions decreases chances for successful transplantation.

The potential influence of early and delayed marrow transplantation on the survival of patients with severe aplastic anemia based on this and other comparable series is shown in Table 4. The data, albeit hypothetical, suggest that early transplantation should increase ultimate survival by decreasing pretransplant mortality and other nonlethal complications (sensitization, debility, etc.) that inhibit successful transplantation.

Our present approach to the newly diagnosed patient with aplastic anemia is summarized in Fig. 2. We hypothesize that early transplantation increases chances for successful marrow reconstitution. In addition, the 3-wk waiting period between presentation and the onset of pretransplant immunosuppression allows time for evidence of early spontaneous recovery to appear. During this
interval, corticosteroids may produce rapid improvement in patients actually leukemic and may also decrease capillary fragility.

As shown in this paper, there exist a number of patients with aplastic anemia unresponsive to standard medical management. These may be the worst patients, referred to us for transplantation only when all other approaches failed. However, we suspect that the sample reported here is truly representative of the spectrum of severe aplasia. Retrospective analysis of our experience and that of other centers suggests that early marrow transplantation, despite its mortality, unknown long-term consequences, and cost, may provide an improved outlook for these patients. Only a controlled prospective study will document this concept. Such an investigation is now underway.

REFERENCES

22. Thomas ED: Personal communication


25. Yankee RA: HLA-antigens and platelet therapy. Presented at Conference on Platelets, St. Elizabeth's Hospital, Boston, June 7-9, 1973 (to be published)

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