Severe Aplastic Anemia: A Prospective Study of the Effect of Early Marrow Transplantation on Acute Mortality

By Bruce M. Camitta, E. Donnall Thomas, David G. Nathan, George Santos, E. C. Gordon-Smith, Robert P. Gale, Joel M. Rappeport, and Rainer Storb

A prospective randomized trial of therapy for severe aplastic anemia was designed to compare early bone marrow transplantation with conventional treatments. All patients with a sibling matched at the major histocompatibility region were transplanted. Transplantation was performed within 17-100 (median 33) days of original diagnosis. Conventional treatments included transfusion support with or without androgens. Twenty-four of 36 patients entered on the transplant arm are alive after 4-20 (median 9) mo with full marrow reconstitution. Only two are limited by chronic graft-versus-host disease. In contrast only 12 of 31 conventionally treated patients are alive. Six of these survivors have improved, five incompletely. The 19 nontransplant deaths have occurred within 1-11 (median 3) mo of diagnosis. Compared to nontransplant regimens, early transplantation more effectively restores normal marrow function and decreases the acute mortality of severe marrow aplasia ($p = 0.006$). Pending longer follow-up, early marrow transplantation appears to be the most effective available treatment for severe aplastic anemia.
In order to determine the relative merits of different therapies for severe aplastic anemia, a cooperative prospective randomized trial was designed. The objectives were (1) to compare the efficacy of early bone marrow transplantation with more conventional treatment, and (2) to evaluate (in patients given transfusion support) the role of androgens in treatment of severe marrow aplasia. This communication reports results relevant to the first question.

**Materials and Methods**

**Definition**

To qualify as severely aplastic, patients had to have at least two of the following three peripheral blood values: (1) granulocytes <500/cu mm (2) platelets <20,000/cu mm and (3) reticulocytes <1% (corrected for hematocrit). In addition the marrow had to be either markedly hypoplastic (<25% of normal cellularity) or moderately hypoplastic (25%–50% of normal cellularity with <30% of remaining cells being hematopoietic) as estimated from biopsies.

**Histocompatibility Typing**

As soon as possible after diagnosis the patient and all members of his/her family were typed for the serologically detected HLA-A and HLA-B antigens. Cells from HLA-A/HLA-B matched siblings were then studied with patient cells in mixed leukocyte culture (MLC). Nonreactivity confirmed matching at the HLA-D locus. All donors were compatible with recipients in these tests.

**Eligibility and Patient Randomization**

Only newly diagnosed cases of severe aplastic anemia were eligible for this study. Patients were observed for 10 days to determine the presence of an underlying illness, to establish baseline blood counts, to detect early spontaneous hematologic improvement, and to complete histocompatibility typing. During this time prednisone (10 mg/sq m/day) was given, in an attempt to detect underlying leukemia. Patients with pancytopenia due to nutritional deficiency, malignancy, preleukemia, myelofibrosis, or Fanconi's anemia and patients with other life-threatening diseases were excluded from the study.

The outline of the protocol is given in Fig. 1. All patients with matched siblings were scheduled to receive a marrow transplant. Patients without matched siblings were randomized to one of three arms: (1) no androgen, (2) oral androgen (oxymetholone), or (3) intramuscular androgen (nandrolone decanoate).

![Fig. 1. Randomization: See text for nontransplant rerandomization criteria.](https://example.com/fig1.png)
SEVERE APLASTIC ANEMIA

PRETRANSPLANTATION

<table>
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<tr>
<th>AGENT</th>
<th>DOSE</th>
<th>SCHEDULE</th>
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<tbody>
<tr>
<td>A. CYCLOPHOSPHAMIDE</td>
<td>50 mg/kg</td>
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<tr>
<td>DONOR BUFFY COAT</td>
<td>1 unit</td>
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B. CYCLOPHOSPHAMIDE 50 mg/kg
ALG 12.5 mg/kg
PROCARBAZINE 12.5 mg/kg

Fig. 2. Pre- and post-transplantation immunosuppression regimens. A: Standard pretransplant preparation. B: Preparations of patients presensitized to their donors or who had rejected a prior marrow graft. Antilymphocyte serum could be used in place of antilymphocyte globulin (+).

POST TRANSPLANTATION

METHOTREXATE
15 mg/m² DAY 1 THEN
10 mg/m² DAYS 3, 6, 11–WEEKLY FOR 90 DAYS

Transplantation Procedures

Protocols for pretransplant immunosuppression are given in Fig. 2. The rationales for and details of doses and schedules used have been previously published. Cyclophosphamide (CY) was used alone for conditioning for engraftment, except in patients thought to be presensitized to their donors or who had rejected a first marrow transplant. In these latter instances, antithymocyte globulin or serum (ATG or ATS) and procarbazine (PCB) were also given. Donor marrow was obtained utilizing standard techniques. Methotrexate was given after transplantation to ameliorate potential graft-versus-host disease (GVHD). Criteria for GVHD have been presented elsewhere.

Patient Care

Transplanted and nontransplanted patients were given transfusions of blood components as required. HLA-matched products were utilized for refractory patients (when available). All patients were watched carefully for infection and treated with appropriate antibiotics when infection occurred. Nontransplanted cases were managed as outpatients except for the frequent complications. Prednisone, 10 mg/sq m/day, was continued in a few nontransplanted cases at the discretion of the patient’s physician. Isolation procedures for transplanted patients varied from simple reverse precautions to laminar air flow isolation with sterile diet and gut sterilization depending on institutional facilities.

Criteria for Improvement

Complete response was defined as the return of all blood counts to normal values. Partial response meant improvement so that the patient no longer qualified for severe status and no longer required transfusions.

Informed Consent

Informed consent of the patient, the donor, and the involved family members was obtained utilizing procedures and consent forms approved by the ethical review committees of the various institutions involved.

RESULTS

The transplanted and nontransplanted patients were compared for factors felt to have prognostic significance in aplastic anemia (Table 1). The groups were comparable except for four patients over the age of 45 in the nontransplant group.
Table 1. Pretreatment Patient Characteristics

<table>
<thead>
<tr>
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<th>Transplanted</th>
<th>Nontransplanted</th>
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<tbody>
<tr>
<td>Age (yr)</td>
<td>16 (1-43)*</td>
<td>13 (0.5-77)</td>
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<tr>
<td>Male/female</td>
<td>19/17</td>
<td>21/10</td>
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<tr>
<td>Etiology</td>
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<tr>
<td>Idiopathic</td>
<td>26</td>
<td>23</td>
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<tr>
<td>Posthepatitis</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Drug-induced</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Insecticide</td>
<td>3</td>
<td>—</td>
</tr>
<tr>
<td>Interval of symptoms-diagnosis (wk)</td>
<td>3 (0-17)</td>
<td>3 (1-17)</td>
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<tr>
<td>Initial hematologic values</td>
<td></td>
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<tr>
<td>PMN/cu mm</td>
<td>200 (0-1500)</td>
<td>240 (0-2000)</td>
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<tr>
<td>Platelets/cu mm</td>
<td>$6 \times 10^5$ (1-23)</td>
<td>$5 \times 10^5$ (1-23)</td>
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<td>Reticulocytes (%) t</td>
<td>0.1 (&lt;0.1-1.4)</td>
<td>0.3 (&lt;0.1-1.5)</td>
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<tr>
<td>Nonmyeloid marrow cells (%)</td>
<td>85 (40-99)</td>
<td>90 (30-99)</td>
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* Numbers in parentheses represent the range of values.
† Corrected for hematocrit.

Transplanted Patients

Thirty-six patients entered the transplant arm during the first year of the study (Table 2). Twenty-six received CY alone and ten CY plus ATG and PCB in preparation for engraftment. Although the protocol specified that pretransplant immunosuppression begin by day 21, suppression usually began later (median 33, range 12-97 days). These delays were due to practical problems involved in diagnosis, histocompatibility typing, informed consent, and (not infrequently) waiting for an available bed at a transplantation center.

Two patients died of sepsis during pretransplant immunosuppression. The remaining 34 patients were successfully engrafted. Twenty-four of these 34 (67% of all patients entered on the transplant arm) are now alive with complete marrow restoration after 4-20 (median 9) mo (Table 3). Two long-term survivors are physically limited by severe chronic GVHD. The others returned to regular activities within 3-12 mo after transplantation. In this limited number of patients, there was no correlation of transplant success with patient age or sex, etiology of aplasia, transplant center, or transplantation regimen.

Table 2. Outcome of Transplants

<table>
<thead>
<tr>
<th>Entered</th>
<th>36</th>
<th>Died during immunosuppression</th>
<th>2</th>
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<tbody>
<tr>
<td>Engrafted</td>
<td>34</td>
<td>Died due to infection</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sepsis, GVHD (day 63, 133)</td>
<td>2</td>
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<tr>
<td></td>
<td></td>
<td>Pneumonia, sepsis (day 89)</td>
<td>1</td>
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<tr>
<td></td>
<td></td>
<td>Tuberculosis (day 140)</td>
<td>1</td>
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<tr>
<td>Graft rejection</td>
<td>9</td>
<td>Died before retransplantation</td>
<td>1</td>
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<tr>
<td></td>
<td></td>
<td>Spontaneous recovery</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Retransplanted</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Died: no take</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Engrafted</td>
<td>2</td>
</tr>
<tr>
<td>Alive with full marrow recovery</td>
<td>24</td>
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Table 3. Current Status of Study Patients

<table>
<thead>
<tr>
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<th>Complete Response</th>
<th>Partial Response</th>
<th>No Improvement</th>
<th>Died</th>
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<tr>
<td>Transplanted</td>
<td>24</td>
<td>0</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>Nontransplanted</td>
<td>1</td>
<td>5</td>
<td>6</td>
<td>19</td>
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</table>

Improvement (CR + PR): transplanted versus nontransplanted, \( p < 0.001 \).

Eight patients rejected their grafts within 4-5 wk after transplantation. Another lost marrow activity during adenine arabinoside therapy begun 23 days post-transplantation for disseminated Herpes zoster. One of these nine died before retransplantation could be attempted. A second patient developed increasing granulocytes during retransplant immunosuppression with ATG and PCB. CY and marrow were not administered. Complete autologous (documented by sex chromosome analysis) marrow recovery ensued. Seven patients who rejected their initial grafts were retransplanted with two successes.

Nontransplanted Patients

Thirty-one patients were assigned to nontransplant regimens: 7 NO, 17 PO, and 7 IM androgens. Results to date have been similar in these small groups and they are reported together (Table 3). Seven patients improved, (one complete and six partial), but one partial response was only transient. Responses began from 1 to 3 mo after randomization. Each responder showed improvement in all three cell lines. Compared to transplanted patients, the response rate in nontransplanted patients was significantly decreased \( p < 0.001, \) Wilcoxon.

Nineteen nontransplanted patients died. Time to death was 1-11 (median 3) mo after randomization. The cause of death was hemorrhage in ten, sepsis in seven, and a combination of sepsis plus hemorrhage in two. Figure 3 is a life-table plot of survival of transplanted and nontransplanted patients. Compared with transplanted patients, mortality in nontransplanted patients was significantly increased \( p = 0.006, \) Wilcoxon.

Fig. 3. Life table plot of the effect of treatment on survival in severe aplastic anemia. Triangles indicate duration of follow-up of current survivors.
Nonrandomized Patients

Two patients improved before randomization. One relapsed after 2 mo and died of hemorrhage. The second relapsed after 4 mo and remains aplastic.

DISCUSSION

The present study has confirmed the short lethal course of most patients with severe aplastic anemia when treated with conventional nontransplant regimens. In contrast, mortality in transplanted individuals was significantly decreased. Although we did not evaluate early versus late transplantation, the results reported here were superior to the prior series in which most patients were transplanted after failure of conventional treatment. It would appear that the small chance of early recovery on conventional therapy was probably more than offset by the morbidity, mortality, and sensitization by transfusion that delay must entail.

This study did not evaluate the role of intensive support in the management of severe aplastic anemia. Marrow transplant patients require intensive support during pretransplant immunosuppression and during the 2-3-wk period of total aplasia before the transplanted marrow begins to function. Some of our transplanted cases were managed in protected environments and received oral nonabsorbable antibiotics. Such regimens have decreased morbidity in myelosuppressed leukemic patients, but their value in a transplant setting is not yet established. However, since hematologic recovery in severe aplasia is usually slow, if it occurs at all, short periods of isolation would probably have little effect on eventual mortality of nontransplanted patients. The physical, financial, and personnel resources required for trials of long-term intensive environmental support of large numbers of nontransplanted severely aplastic patients are not currently available.

The better outcome of our transplanted patients might also be attributed to superior granulocyte and platelet transfusion support available at transplant centers. However, nontransplanted individuals managed at transplant centers fared no better than similar patients treated elsewhere. However, it is still possible that mortality in nontransplanted severe aplastic anemia could be decreased by wider availability of HLA matched nonfamily blood product support.

The importance of long-term follow-up of surviving patients with aplastic anemia must be emphasized. Patients who recover after conventional treatment may relapse and die months or years later. Similarly, although promising in the short-term management of severe aplasia, transplantation may have adverse long-term sequelae that have not yet been encountered. Nevertheless, in the Seattle series of 23 aplastic anemia patients who survived more than 1 yr after allogeneic marrow transplantation, only one patient has died, one has chronic GVHD, and one has almost completely recovered from chronic GVHD. The other 20 patients are in good health with normal marrow function after 2 to 4½ yr follow-up.

Despite the above caveats, this study shows that prompt bone marrow transplantation significantly decreases the early mortality of severe aplastic anemia.
SEVERE APLASTIC ANEMIA

That finding in itself is an important reason for application of this complex treatment in a devastating disease.

REFERENCES


APPENDIX: CONTRIBUTING INSTITUTIONS AND PHYSICIANS

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<tr>
<th>Institution</th>
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<td>E. Forman</td>
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<td>R. Epstein, W. Fried</td>
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