FOR MOST OF ITS HISTORY, aplastic anemia has had a dire reputation. In the decades after Ehrlich's original description of the disease a century ago, many patients died simply of anemia. The introduction of blood product support and antibiotics improved the care of patients, but in Wintrobe's 1956 textbook, aplastic anemia could still be described as "progressively, inexorably, and more or less rapidly fatal... Death ensues in the course of a few weeks or life may linger as long as six months." Today, the disease can be cured or ameliorated in most patients. By the end of the 1960s, replacement of the characteristically empty bone marrow by a marrow transplant from a sibling donor was shown to be curative in studies performed by Thomas et al in Seattle and in several European centers. In the 1970s, the observation of autologous marrow recovery after treatment with antilymphocyte sera suggested that nonreplacement therapy could restore marrow function. Increasingly refined transplant regimens and intensified immunosuppressive therapy, as well as improved transfusion support and modern antimicrobials, have produced spectacular hematologic improvement and long-term survival rates, which will be described below.

Unfortunately, these advances are unavailing to patients with severe pancytopenia observed for weeks for the rare spontaneous remission, prescribed useless long courses of corticosteroids, or subjected as an individual to a test course of the newest growth factor. Applications of remedies of doubtful or unproven value are dilatory strategies with often disastrous consequences in a disease infamous for its cascading complications. Even the experienced physician—and well-informed patient—face therapeutic dilemmas in aplastic anemia, most particularly the decision between allogeneic transplantation and immunosuppression and the consideration of transplant from an unrelated marrow donor.

We deal here with current treatment issues in severe aplastic anemia (severity defined by blood count criteria'). Readers are referred to recent monographs for fuller discussions and extensive bibliographies.4,4

PATHOPHYSIOLOGY OF APLASTIC ANEMIA

Hematopoietic activity is reduced in all patients with aplastic anemia, as reflected in marrow histology, low numbers of CD34+ cells, and poor colony formation in functional progenitor assays.9,10 Bone marrow failure may directly result from dose-dependent destruction of stem cells, as caused by radiation, cytotoxic chemotherapy, and benzene. In some rare individuals, abnormal drug metabolism might produce toxic intermediate compounds that harm marrow cells, but evidence for such a mechanism in patients has been elusive. In a large epidemiologic study, only about one quarter of cases were attributed to drug use.1 A significant history of radiation, benzene, or chloramphenicol use is now very unusual among patients with community acquired aplastic anemia.

In theory, marrow failure in aplastic anemia could be the consequence of damage either to hematopoietic cells or to the stromal cells required for their production. However, most of the evidence points strongly to effects on hematopoietic cells, and stromal cell function and growth factor production are normal in almost all patients with aplastic anemia.1,12

Much, perhaps most, acquired aplastic anemia appears to be secondary to immune system mediated destruction of marrow cells. The immune hypothesis, first inferred from the response of patients to antilymphocyte sera by Mathé et al and from coculture experiments performed at Sloan-Kettering, has been supported by a large variety of subsequent laboratory experiments and clinical observations. Hematopoietic failure in aplasia is likely mediated by cytotoxic T lymphocytes that are detectable in blood and marrow.14 These cells produce the cytokines γ-interferon and tumor necrosis factor-β, both of which broadly inhibit in tissue culture both progenitor cell growth and the generation of long-term culture-initiating cells, an in vitro surrogate for the stem cell.15 The action of inhibitory cytokines is not merely suppressive but destructive, inducing cell death in the CD34+ compartment, probably through Fas-mediated apoptosis.16 γ-Interferon, which is not a normal marrow factor, is produced in the marrow of most patients with acquired aplastic anemia.17,18 The potent activity of a locally secreted inhibitor molecule was shown in recent experiments in our laboratory. Stromal cells, engineered by transduction of the
γ-interferon gene to constitutively express low levels of the cytokine, completely suppressed hematopoiesis at measurable levels about 100-fold lower than equivalently inhibitory concentrations of exogenous γ-interferon (Selleri, Maciejewski, and Young, unpublished data). The large number of clinical associations with aplastic anemia—drugs, viruses, pregnancy, and graft-versus-host disease (GVHD)—suggest that a variety of events can activate the immune system to cause marrow aplasia. Increased representation of certain histocompatibility antigens among aplastic anemia patients implicates host genetic factors in the peculiar immune response to these agents.19,20

The pathophysiology of the disease suggests two approaches to therapy: replacement of deficient stem cells (and coincidentally of the immune system) by bone marrow transplantation or suppression of a destructive immunologic process. Unfortunately, neither measures of stem cell number nor immune system dysfunction are clinically useful guides to treatment selection in individual patients.

ALLOGENEIC BONE MARROW TRANSPLANTATION

In almost all cases the donor is a full sibling, identical at HLA A, B, and DR histocompatibility loci with the recipient. The 25% probability of finding a fully compatible match within the recipient’s family makes allogeneic transplantation available to only a minority of patients.

Bone marrow transplant data come from two sources. First, a few hospitals accrue sufficient aplastic patients to generate case series. Single-center studies can evaluate specific research protocols, and both protocol design and patient care gain from the high level of expertise in such specialized units. Selection bias before admission, based on the presence of adverse prognostic factors or financial status, is possible, but analysis of current patient data suggest that most transplant centers include poor-risk patients in their program (older, heavily transfused, or more chronic cases). Transplant data also have been derived from the International Bone Marrow Transplant Registry and the European Group for Bone Marrow Transplant. Registries are observational data bases, and they usually include diverse patient populations and protocols, which vary with respect to conditioning regimen and GVHD prophylaxis. Analysis of the data base can be complicated by the heterogeneity of treatment approaches, but registries also allow comparison of different therapeutic strategies. Selection bias may be introduced because reporting is voluntary. However, their substantial sample size and high level of participation make registries likely to accurately represent treatment outcomes in practice. Large patient numbers and long follow-up facilitate statistical analyses even if early mortality is high and late events infrequent.

Despite the differences between single-center and registry data, the results of bone marrow transplantation in aplastic anemia from these two sources are in broad agreement (Table 1). Consideration of the confidence intervals in actuarial survival estimates suggest that the figures from the best single-center trials may not differ significantly from registry numbers. Allogeneic bone marrow transplantation is effective in restoring normal hematopoiesis in the majority of patients to whom it is applied. The main issues are whether mortality for an unselected group is greater than 30% or less than 10% and how these differences relate to variations in treatment management. Recent results, whether from single centers or registries, show improvement over earlier published reports. In Seattle, survival increased from about 45% between 1970 and 1976 to 60% from 1977-1988 to about 90% in 1988-1993.21 Similarly, for the European Group for Bone Marrow Transplantation, survival increased from 43% in 1970-1979 to 63% in 1980-1989 and 72% in 1990-1994. These improvements have been attributed to multiple factors: more intensified conditioning regimens to prevent graft rejection, the use of cyclosporine both to improve engraftment and prevent GVHD, better blood product preparation that reduces allosensitization, and improved supportive care with new antimicrobial and antiviral agents. Nevertheless, graft rejection, GVHD, and infection remain limiting factors to the success of transplantation.

Graft rejection. Hematopoietic failure because of either failure to engraft or engraftment followed by rejection is a major complication in marrow transplant for aplastic anemia, related in part to insufficient immunosuppression of the recipient and perhaps also to the underlying immune pathophysiology of the disease. Graft failure has a high mortality. Second transplants are only successful in one third of patients, and only rarely do patients recover autologous hematopoiesis.23,24

Engraftment requires an adequate stem cell dose, usually provided by a single marrow harvest that includes donor T lymphocytes in the inoculum.25 Graft rejection is related to presensitization of the recipient to minor histocompatibility antigens of the donor by blood product transfusion or pregnancy. Untransfused or minimally transfused patients have engraftment rates similar to those of identical twin recipients.26 Although transplantation in the untransfused patient may be optimal, in reality, transfusion in the severely pancytopenic patient is rarely avoidable. The impact of transfusion allosensitization may have been exaggerated. In one registry survey, transfusion of limited numbers of blood products (40 U or less) had only a modest impact on the rate of graft failure.27 Probably the introduction of filtered, leukocyte-depleted red blood cell and platelet products has contributed to reducing pretransplantation alloimmunization.28

Graft rejection rates have decreased over time. Historically, combinations of cyclophosphamide and irradiation were used in the conditioning regimens to ensure engraftment. Irradiation (and inevitably radiomimetic agents), although reducing deaths from graft failure, increase post-transplant mortality and cause infertility and late malignant disease.29 More acceptable and currently successful protocols that reduce graft failure with less toxicity incorporate prolonged used of cyclosporine postransplant23 and antithymocyte globulin (ATG) in the conditioning regimen.31,34,35

GVHD. GVHD is a major cause of late mortality and morbidity, both as an immediate and a delayed consequence of allogeneic bone marrow transplantation. Up to 80% of matched sibling bone marrow recipients develop some degree of acute GVHD in the first 3 months after transplant, and acute GVHD contributes to mortality in about 10% of recipients. Chronic GVHD develops in up to 50% of patients.
surviving more than 3 months after transplant, in 20% as a serious complication, and in 5% as a fatal event. Even in recent aplastic anemia transplant series, chronic GVHD was frequent among long-term survivors (Table 2).

GVHD is mediated by donor lymphocytes but much of its biology remains unclear.36 Perhaps because of thymic involution, GVHD increases in frequency and severity in recipients more than 20 years of age. The incidence of acute GVHD increases with age: in a Seattle series, from 26% in children ≤10 years old to 50% to 80% in adults ≥41 years old; in International Bone Marrow Transplant Registry patients from 34% ± 4% in children less than 10 years old to 50% ± 7% in adults ≥40 years old.37 Acute GVHD is itself a powerful risk factor for chronic GVHD, but independently age more than 20 years is also a predictor of chronic GVHD.38 In a recent University of Minnesota analysis, chronic GVHD was three times more frequent in transplant recipients more than 18 years old than in younger patients.39 Among Seattle aplastic anemia patients, the rate of chronic GVHD showed a progressive increase with age (19% for patients 0 to 10 years old, 46% at 11 to 30 years of age, and 90% in patients more than 31 years old).40 The risk of chronic GVHD in children (<18 years old) with aplastic anemia is now probably about 10%.41

The increased risks of GVHD with age contribute to the poorer survival posttransplant in older patients (Table 2). For transplants reported to the International Bone Marrow Transplant Registry between 1986 and 1992, the total 5-year survival was 66%, but for patients more than 25 years of age, it was less than 60%, whereas for children less than 16 years old survival was about 75%.42 Bone marrow transplantation for aplastic anemia in patients more than 45 years of age has been only occasionally successful.43 Cyclosporine prophylaxis appears to have reduced the incidence of both acute and chronic GVHD in single-center studies as well as in registry comparisons.22,42,44 Reduction in the mortality from chronic GVHD by aggressive immunosuppression may ultimately blunt the influence of age on GVHD.

In summary, excellent survival and low morbidity in younger patients make allogeneic bone marrow transplantation the treatment of choice for children and adolescents. Patients older than the age of about 40 years have a high risk of transplant-related morbidity and mortality. Young adults in the intermediate age group have a reasonable opportunity for cure with a bone marrow transplant but also face more complications than children. In addition to age, a prolonged interval between diagnosis and transplant, multiple transfusions, and serious infections before transplant are risk factors.

### IMMUNOSUPPRESSION

Antilymphocyte globulins (ALG). The mechanism of action of antilymphocyte sera and cyclosporine is almost certainly immunosuppressive. ALG is cytolytic of T cells and

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### Table 1. Recent Results of Allogeneic Bone Marrow Transplantation in Aplastic Anemia

<table>
<thead>
<tr>
<th>Institution</th>
<th>Years</th>
<th>N</th>
<th>Age (yr)</th>
<th>Conditioning Rx</th>
<th>GVHD Px</th>
<th>AGVHD (%)</th>
<th>CGVHD (%)</th>
<th>Actuarial Survival (%)</th>
<th>F/U (yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hôpital St. Louis†</td>
<td>1980-89</td>
<td>107</td>
<td>5-48 (19)</td>
<td>CY + TAI</td>
<td>MTX, CSA, or MTX + CSA</td>
<td>3</td>
<td>68 ± 10 (5yr)</td>
<td>1-10 (3.75)</td>
<td></td>
</tr>
<tr>
<td>Johns Hopkins*</td>
<td>1984-91</td>
<td>21</td>
<td>5-46 (19)</td>
<td>CY + TLI</td>
<td>MTX + CSA</td>
<td>17</td>
<td>78 ± 15 (5yr)</td>
<td>0.5-5 (2.3)</td>
<td></td>
</tr>
<tr>
<td>Hutchinson*</td>
<td>1988-1993</td>
<td>39</td>
<td>5-66 (24.5)</td>
<td>CY + ATG</td>
<td>MTX + CSA</td>
<td>5</td>
<td>92 (3yr)</td>
<td>0.8-6 (2.5)</td>
<td></td>
</tr>
<tr>
<td>IBMT</td>
<td></td>
<td></td>
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</table>

Abbreviations: Px, prophylaxis; Rx, therapy; AGVHD, acute GVHD; CGVHD, chronic GVHD; CY, cyclophosphamide; MTX, methotrexate; CSA, cyclosporine; TBI, total body irradiation; TAI, total abdominal irradiation; TLI, total lymphoid irradiation; ATG, antithymocyte globulin; IBMTR, International Bone Marrow Transplant Registry; EGBMT, European Group for Bone Marrow Transplantation.

Especially when results are reported early, Kaplan-Meier estimates may be higher than ultimate actual survival figures. For late complications such as chronic GVHD, prevalence in the susceptible population is the relevant figure, to correct for censoring due to death; for the first four studies quoted, the percentages represent the actual prevalence in the population at risk (either explicit in the publication or extracted from the results), and for the Seattle study, the stated actuarial risk is quoted.

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### Table 2. Age and Survival After Bone Marrow Transplantation

<table>
<thead>
<tr>
<th>Institution/Group, Year</th>
<th>N</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hutchinson, 1984†</td>
<td>130</td>
<td>K-M, 2 yr</td>
</tr>
<tr>
<td>Minnesota, 1987†</td>
<td>58</td>
<td>K-M, 6-8 yr</td>
</tr>
<tr>
<td>UCLA, 1990*</td>
<td>29</td>
<td>K-M, 5 yr</td>
</tr>
<tr>
<td>IBMTR, 1993*</td>
<td>737</td>
<td>K-M, 5 yr</td>
</tr>
<tr>
<td>EGBMT, 1994†</td>
<td>540</td>
<td>K-M</td>
</tr>
</tbody>
</table>

Abbreviation: K-M, Kaplan-Meier estimate.
both antilymphocyte globulins and cyclosporine inhibit T-cell function, especially the production of suppressive lymphokines. ALG administration rapidly reduces circulating lymphocytes, usually to less than 10% of starting values, and when total lymphocytes return to pretreatment values months later, activated lymphocyte numbers in recovered patients remain decreased.\(^47\) \(^48\) Antilymphocyte preparations in vitro stimulate T-cell proliferation and promote secretion of some growth factors.\(^49\) \(^50\) However, these actions are probably peripheral to the therapeutic effect, because growth factors are abundant in untreated aplastic anemia. Improvements in response rates have largely been caused by intensification of immunosuppression with cyclosporine rather than the addition of growth factors.

In contrast to bone marrow transplantation, in which engraftment results in the establishment of normal (donor) hematopoiesis, successful immunosuppressive therapy only occasionally leads to rapid normalization of blood counts. More commonly, levels of hemoglobin, neutrophils, or platelets improve gradually over months or even years to levels sufficient to prevent spontaneous bleeding, bacterial and fungal infection, and the need for red blood cell transfusions.\(^52\) Possible reasons for slow or partial recoveries include continued inhibition of marrow by lymphocytes or irreversible stem cell loss. The assessment of clinical recovery is not simple and complicates the interpretation of clinical trials. Transfusion independence may be a subjective measure of response, because hematologists vary in their criteria for administration of blood products and individual patients tolerate anemia and thrombocytopenia differently. Blood counts are affected by continued transfusion. Even modest improvement in one or two lineages can be clinically significant, eg, even marginally higher neutrophil numbers can profoundly alter the probability of survival, whether or not transfusion independence is also achieved. For these reasons, hematologic recovery or response rates have been derived from absolute increases in blood counts, transfusion-independent status, or failure to satisfy the criteria for severe disease.

Despite lack of agreement on these criteria, a review of results with immunosuppression in the early 1980s suggested that about 45% of patients with severe disease responded to ALG,\(^53\) including randomized controlled\(^54\) and large multicenter trials\(^55\) of ATG in the United States. European preparations against thoracic duct lymphocytes (ALG; from Merieux [Lyon, France] and the Swiss Serum Institute [Berne, Switzerland]) appeared to have equivalent efficacy to ATG (Upjohn, Kalamazoo, MI) available in the United States. In vitro, there are no major differences between ATG and ALG or among individual lots in cytolytic activity or in T-cell antigens recognized.\(^56\) \(^58\) Differences in treatment regimens also do not appear to appreciably affect response rates. Some early protocols used 10 to 28 daily intravenous infusions, but a short course (40 mg/kg/day for 4 days) is equally effective and less toxic, especially for induction of serum sickness.\(^59\) Although clearly active in aplastic anemia, ATG and ALG have generally not been very useful in children or in patients who are severely neutropenic\(^60\) \(^62\) (very severe cases, with absolute neutrophil counts <200/μL, have the poorest prognosis\(^63\)).

**Cyclosporine.** Cyclosporine had been reported anecdotally to produce responses in some patients with aplastic anemia.\(^64\) In more systematic studies, cyclosporine produced about a 50% response rate in patients who were refractory to ATG or ALG treatment.\(^65\) \(^66\) Most hematologic improvement occurred within a few months of starting therapy and was usually sustained after cyclosporine was discontinued; however, recovery was sometimes dependent on continued cyclosporine administration. A French multicenter trial attempted a direct comparison of cyclosporine to ALG as initial treatment for aplastic anemia and found no difference in outcome, but the response rates to either agent were poor, probably because of the low doses of cyclosporine and ALG used.\(^67\) Although in some studies lower doses have been effective,\(^68\) best results have been seen with high doses of cyclosporine (12 mg/kg/d for adults and 15 mg/kg/d for children). These regimens require frequent monitoring of blood cyclosporine levels and dose adjustment for creatinine levels. Serious complications from cyclosporine include hypertension, seizures (perhaps related to hypomagnesemia), and *Pneumocystis carinii* infection. Responses have been sufficiently consistent and impressive that cyclosporine has been enthusiastically advocated over antilymphocyte sera by some European investigators.\(^69\)

**Intensive immunosuppression.** Clinical trials that combined cyclosporine and ALG followed from the observation of clinical efficacy in aplastic anemia of each agent alone. Joining their different mechanisms of action, lymphocytotoxicity provided by ATG or ALG and functional block of lymphocyte activation and activity by cyclosporine, would produce more intensive immunosuppression. Recent trials have indicated that intensive immunosuppression is superior to ALG or ATG alone in severe aplastic anemia (Table 3). In a large German multicenter protocol, patients were randomized between ALG and ALG plus cyclosporine in full doses.\(^70\) Added cyclosporine greatly increased the hematologic response rates (65% v 39% at 3 months and 70% v 46% at 6 months in all patients). The combined regimen more than doubled the response rate for very severe disease (65% v 31% for ALG alone), and actuarial survival at 41 months also was higher (80% v 44%). Responses occurred sooner and were more complete and relapses were less frequent with combined therapy. Survival for all patients in the two groups was not different, perhaps because of the routine addition of cyclosporine to nonresponders in the control (ALG only) arm at 3 months. Similar results were found when ALG was compared with ALG plus cyclosporine in 42 severe and moderate Korean aplastic anemia patients (70% v 43% response rates at 6 months).\(^71\) In a study at the National Institutes of Health Clinical Center of untreated severe aplastic anemia, cyclosporine plus ATG produced hematologic remissions in almost 80% of patients, more than twice the remission rate for matched historical controls.\(^72\) Severely neutropenic patients had hematologic response and survival rates indistinguishable from patients with granulocyte numbers greater than 200/μL. Children, who have been poor responders to ATG or ALG alone, actually had a higher response rate to combined therapy than did adults (<20 years of age, 86% at 1 year; ≥20 years of age, 72%). Children
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have done well in other, small pilot studies of intensive immunosuppression. In a recent prospective European cooperative trial, intensive immunosuppression was combined with granulocyte colony-stimulating factor (G-CSF) therapy. Almost all patients showed hematologic responses, and the actuarial probability of transfusion independence at 18 months was 97%. Actuarial survival at almost 3 years was 92% (there were 3 early deaths and 4 treatment failures among the 40 patients treated), and even among very severe cases the rate was 86%. Interpretation of the contribution of G-CSF is confounded by the inclusion of 20 patients who were retreated with ALG.

Corticosteroids. Methylprednisolone in modest doses, usually 1 mg/kg/d, is administered during ALG and ATG therapy to ameliorate serum sickness. Low-dose corticosteroids are not effective treatment in aplastic anemia, and their role in stabilizing vascular integrity and preventing bleeding is quite unproven. Extremely high doses of methylprednisolone (20 to 50 mg/kg/d) can induce hematologic responses in aplastic anemia but are not preferable to either ALG or cyclosporine. The purported benefit of combining ALG and extremely high doses of corticosteroids was not confirmed in a controlled trial. Corticosteroids at even modest doses have significant toxicities; the development of aseptic necrosis of femur or humerus are particularly unpleasant complications in the thrombocytopenic aplastic anemia patient.

Relapse and evolution of clonal disease. For all immunosuppressive therapy in 358 European patients, the risk of relapse at 14 years was 35%. The same proportion of NIH patients treated with ATG and cyclosporine also relapsed. Relapse may be less frequent when patients are treated promptly after diagnosis. The majority of relapsed patients respond again to immunosuppression, and their prognosis appears similar to those cases who do not relapse.

Evolution of aplastic anemia to another hematologic disease can occur years after a successful response to immunosuppression. Laboratory evidence of paroxysmal nocturnal hemoglobinuria (PNH) is most common, ie, 13% in a large retrospective European survey but higher (57% in Basel) or lower (<9% in Seattle) in smaller series. The significance of these figures is now uncertain, because a high proportion of aplastic anemia patients at presentation have flow cytometric evidence of defective expression of glycolipidophosphoinositol-linked proteins (the Ham test is insensitive in aplastic anemia, not only because patients are so commonly transfused with red blood cells but because granulocytes may manifest the defect more frequently). Posttreatment PNH is often subclinical and rarely associated with severe hemolysis or thrombotic events. More serious complications are myelodysplasia and leukemia. In a European study, the 10-year cumulative incidence rate was 9.6% for myelodysplasia (without leukemia) and 6.6% for acute leukemia. Myelodysplasia may possibly be milder in long-term survivors of aplastic anemia than as a primary diagnosis, but some patients progress rapidly to leukemia. In addition to clonal bone marrow disorders, aplastic anemia patients postimmunosuppression and after bone marrow transplantation (especially with radiation in the conditioning regimen) have an increased rate of occurrence of malignant tumors, ie, 2% to 3% after a decade.

ROLE OF HEMATOPOIETIC GROWTH FACTORS

As described above, neither deficient stromal cell function nor growth factor production is central to the etiology of aplastic anemia. Administered growth factors probably increase blood counts by stimulating the existing committed progenitor cell pool. G-CSF and granulocyte colony-stimulating factor (GM-CSF) usually affect neutrophil numbers only, and improvement is generally proportional to the patient’s initial neutrophil count. Granulocyte numbers often decline despite continued treatment, and higher cell counts, if sustained, are dependent on continued factor administration. However, a Japanese multicenter trial of chronic G-CSF therapy showed marked increases in neutrophil count in almost all patients, and 10 of 27 patients also showed improvement in anemia, with 3 having higher platelet counts as well. Interleukin-3, alone or in combination with GM-CSF, has had even less impact on myelopoiesis than G-CSF or GM-CSF and little on platelet production. Bilineage and trilineage responses to G-CSF and GM-CSF therapy cited anecdotally may represent delayed improvement after immunosuppression or spontaneous remission. Despite the lack of objective support for their use, growth factors are now frequently offered to patients with severe bone marrow failure, before definitive therapy by marrow transplant or immunosuppression, a practice appropriately deprecated as wasteful and dangerous by a group of European experts. Nevertheless, G-CSF and GM-CSF can shorten the period of neutropenia postmarrow transplant, and they

<table>
<thead>
<tr>
<th>Study, Year</th>
<th>Regimen</th>
<th>Median Age (range; yr)</th>
<th>Median ANC/μL</th>
<th>Response</th>
<th>Survival</th>
<th>Relapse</th>
<th>Median F/U (d)</th>
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<tr>
<td>German multicenter, 1992</td>
<td>ALG + CSA</td>
<td>43</td>
<td>32 (7-80)</td>
<td>0.48/19%</td>
<td>70% at 6 mo</td>
<td>64% at 41 mo</td>
<td>11%</td>
</tr>
<tr>
<td>EGBMT, 1995</td>
<td>ALG + CSA + G-CSF</td>
<td>40</td>
<td>18 (2-72)</td>
<td>0.19/50%</td>
<td>82% at 1 yr</td>
<td>92% at 34 mo</td>
<td>3%</td>
</tr>
<tr>
<td>NIH, 1995</td>
<td>ATG + CSA</td>
<td>51</td>
<td>28 (3-79)</td>
<td>0.34/42%</td>
<td>78% at 1 yr</td>
<td>86% at 1 yr</td>
<td>18% at 1 yr</td>
</tr>
</tbody>
</table>

Abbreviations: ALG, antilymphocyte globulin; ATG, antithymocyte globulin; CSA, cyclosporine; G-CSF, granulocyte colony-stimulating factor; EGBMT, European Group for Bone Marrow Transplantation; NIH, National Institutes of Health.
may be beneficial when used as an adjunct in an immunosuppressive regimen.74

ANDROGENS

In the 1960s androgens seemed a treatment advance for aplastic anemia, but the early studies grouped moderate and severe as well as acquired and congenital aplastic anemia. Androgens alone as first treatment generally have not been shown to improve survival in severe aplastic anemia,3 if still considered beneficial by some investigators,94,95 An American controlled trial of androgens as an adjunct to ATG showed no benefit,96 and a European randomized protocol showed only higher hematologic response rates but without a survival advantage in a subset of severely affected women.97 Improvement and even androgen dependence can be seen in an occasional patient who has failed immunosuppression, and in this setting they may be useful and are unlikely to be harmful.

Marrow Transplantation from Unrelated Donors

Most aplastic anemia patients lack an HLA-matched sibling donor. Large donor banks can now provide lists of potential donors for patients with more common haplotypes but are far less successful for uncommon HLA types and members of ethnic minorities.26 Even donors phenotypically matched on all three paired HLA A, B, and DR antigens are likely to have both major and minor histocompatibility antigen disparities with the recipient. Serologic testing misses important heterogeneity at the HLA A and B loci, now apparent with molecular typing methods96; identification of major and minor antigen disparity by functional testing is still under development.

Mismatching for a single antigen has a pronounced effect on survival because of graft rejection.100 An intensified conditioning regimen, which includes radiation or an alkylator drug, is required to prevent graft rejection. T-cell depletion of the donor inoculum, effective in preventing GVHD from a matched but unrelated donor, so increases the risk of graft failure as to be precluded in aplastic anemia. A further negative effect is the considerable logistic delay. An average of 4 months is still required to locate a donor, confirm HLA matching, and arrange the harvest, by which time the risks for marrow transplant have increased due to infection and allosensitization.

As a consequence of the higher rates of rejection, GVHD, and infection and the longer interval from diagnosis to procedure, transplantation from an unrelated matched donor has not produced the same excellent outcome as sibling transplant (or transplant from a phenotypically matched family donor; Table 4). Twenty-nine aplastic anemia patients were among 459 unrelated transplants reported from the National Marrow Donor Program; their survival at 2 years was 29%, and 4 of 10 still alive continued to require transfusions.101 In the International Marrow Unrelated Search and Transplant Study (IMUST), underway in several European hospitals, a cohort of unrelated donor transplants has been compared with matched concurrent identical sibling transplants performed at the same centers, all treated for severe aplastic anemia.102 The mean age of recipients of unrelated marrow was 16 years; 36% of the patients were alive at 1 year, with most deaths occurring from the high rate of graft failure (52%), despite intensive conditioning. By comparison, the standard transplant recipients, who were older, showed a 65% 1-year survival rate and less than a 10% rate of graft failure.103 The best results using unrelated donors have been in young children,104 probably because they tolerate the highly toxic chemotherapy used for conditioning and also are less prone to serious GVHD.

The generally poor results of unrelated donor transplantation have been blamed on the deleterious effects of the lengthy search process. As earlier performance of unrelated transplants becomes possible, comparison of unrelated and matched transplants as initial therapy becomes feasible; this high-risk procedure will then also compete more directly with immunosuppressive treatments. A search for a donor should be undertaken early and children especially should be considered as candidates. At present, unrelated transplants would best be performed in experienced units testing their own research protocols or contributing data to a registry.

BONE MARROW TRANSPLANT OR IMMUNOSUPPRESSION?

Immunosuppression as first therapy for patients who lack an HLA-identical sibling and marrow transplantation for children with appropriate donors is uncontroversial (Table 5). A dilemma may exist in selecting the best initial therapy for young to middle-aged adult patients who have compatible siblings. Despite the applicability of both immunosuppression and allogeneic transplant to a small group of patients, views on the merits and disadvantages of each treatment tend to be polarized. At one extreme, transplantation has been advocated for all patients with sibling donors to the age of 55; at the other extreme, immunosuppression has been recommended as first treatment because of the equivalent survival rates.

Marrow transplantation cures aplastic anemia but with a risk of morbidity and mortality secondary to treatment. Immunosuppression induces hematologic improvement—partial correction of blood counts is the rule—but with little
TREATMENT OF SEVERE APLASTIC ANEMIA

Table 5. Treatment Options in Severe Aplastic Anemia

<table>
<thead>
<tr>
<th>Recommended first therapies</th>
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<tbody>
<tr>
<td>Allogeneic bone marrow transplantation</td>
</tr>
<tr>
<td>Sibling donor</td>
</tr>
<tr>
<td>Phenotypically matched family member</td>
</tr>
<tr>
<td>Immunosuppression</td>
</tr>
<tr>
<td>ATG</td>
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<tr>
<td>Cyclosporine</td>
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<td>Combined therapy</td>
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</table>

<table>
<thead>
<tr>
<th>Adjunctive/second therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematopoietic growth factors</td>
</tr>
<tr>
<td>G-CSF</td>
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<td>Androgens</td>
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<td>Unrelated bone marrow transplantation</td>
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<th>Experimental/future therapies</th>
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<tr>
<td>Hematopoietic growth factors</td>
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<td>Stem cell factor</td>
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<td>Combinations of factors</td>
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<td>Thrombopoietin</td>
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<td>Monoclonal antibodies to T cell</td>
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Tocicity and almost no treatment-related mortality. However, successfully treated patients after either therapy may suffer late complications: after immunosuppression, relapse and death due to pancytopenia and transformation to clonal and sometimes malignant hematologic disease; after marrow transplantation, late graft failure, lethal GVHD, and second malignancies. At least initially, marrow transplantation is more expensive than immunosuppression.

In retrospective analyses, immunosuppression and bone marrow transplantation show equivalent beneficial effects on survival in severe aplastic anemia. Survival curves at 6 years of the European Group for Bone Marrow Transplantation are superimposable. The most recent analysis of these data showed a statistically significant survival advantage for transplantation over immunosuppression only among severely neutropenic children (<20 years old), and since 1991 immunosuppression has been equivalent or superior to transplantation for all ages, even among very severe cases (A. Bacigalupo, unpublished data). Series from large single centers may favor immunosuppression (Base105) or transplant (Seattle63), but the differences have not reached statistical significance. The impact of late myelodysplasia and leukemia remains uncertain; a plateau in actuarial survival after immunosuppression has been discerned in some64,106 but not all other65,71 studies. Current long-term survival curves may not reflect relatively recent improvements, notably cyclosporine to intensify immunosuppression and better preparative regimens and cyclosporine in transplantation.107

The excellent results of marrow transplantation in children with HLA-identical siblings and the low mortality and morbidity make transplantation the treatment of choice in the young patient. Transplantation is sufficiently hazardous in patients older than 40 years of age that immunosuppression is generally favored. For other patients, a clear recommendation for one therapy is difficult, perhaps impossible, in the absence of a consensus among experts—or of a prospective comparison of immunosuppression and transplantation, never performed and unlikely to be undertaken. Sometimes a decision will be based on the patient’s insurance status or personality. On medical grounds, immediate transplant should be favored for the younger, relatively untransfused and uncomplicated case. For higher risk or less willing patients, transplant could be reserved to rescue immunosuppression failures.106

FUTURE THERAPIES

Aplastic anemia patients will benefit from general advances in the prevention and treatment of GVHD and the general trend to improved survival after allografting. For nontransplant therapy, the optimal immunosuppressive regimen, especially the desirability of sequential versus combined immunosuppression and the utility of added growth factors should be studied in clinical trials. Prolonged treatment with cyclosporine may be needed to prevent relapses. Other forms of immunosuppression, such as cyclophosphamide, might be useful in patients refractory to ATG and cyclosporine. Monoclonal antibodies to T cells109 and activated T cells110 have produced remissions in occasional patients; specific therapy directed to the pathophysiology of aplastic anemia could include conjugated monoclonal antibodies to T-cell subsets and their lymphokines and competition with soluble receptor molecules (Table 5).

The remarkable achievements in our understanding and treatment of aplastic anemia are the results of clinical research. Further progress depends on the performance of planned trials and access to patient tissue samples. For these reasons, as well as for the experienced care available at tertiary referral hospitals, patients with aplastic anemia should continue to be referred to centers that specialize in bone marrow failure disorders.

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REFERENCES


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99. Santamarina P, Reinsmoen NL, Lindstrom AL, Boyce-Jacino MT, Barbosa JJ, Faraj AS, McGillave PB, Rich SS: Frequent HLA class I and DP sequence mismatches in serologically (HLA-A, HLA-B, HLA-DR) and molecularly (HLA-DRB1, HLA-DQA1, HLA-DQB1) HLA-identical unrelated bone marrow transplant pairs. Blood 83:280, 1994

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The treatment of severe acquired aplastic anemia

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