Published in final edited form as:
*Expert Rev Hematol*. 2011 April ; 4(2): 221–230. doi:10.1586/ehm.11.11.

# Clinical management of aplastic anemia

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## Abstract

Acquired aplastic anemia is a potentially fatal bone marrow failure disorder that is characterized by pancytopenia and a hypocellular bone marrow. Hematopoietic stem-cell transplantation or bone marrow transplantation (BMT) is the treatment of choice for young patients who have a matched sibling donor. Immunosuppression with either anti-thymocyte globulin and cyclosporine or high-dose cyclophosphamide is an effective therapy for patients who are not suitable BMT candidates owing to age or lack of a suitable donor. Results of BMT from unrelated and mismatched donors are improving, but presently this treatment option is best reserved for those patients who do not respond, relapse or develop secondary clonal disorders following immunosuppressive therapy. Efforts are currently underway to both improve immunosuppressive regimens and to expand the application of BMT.

### Keywords

anti-thymocyte globulin; aplastic anemia; bone marrow failure; bone marrow transplantation; cyclosporine; hematopoietic stem-cell transplantation; high-dose cyclophosphamide; paroxysmal nocturnal hemoglobinuria

Aplastic anemia (AA) was first described in a pregnant woman in 1888 [1]. The term now refers to a clinical syndrome defined as pancytopenia with a hypocellular bone marrow in the absence of abnormal infiltration or increased reticulin. AA can be inherited or acquired. The inherited marrow failure syndromes include disorders such as Fanconi anemia, dyskeratosis congenita and Schwachman–Diamond syndrome. Our understanding of the molecular basis for these disorders has progressed in recent years and the genetic defects have been mapped to DNA damage repair mechanisms (Fanconi anemia) [2], telomerase dysfunction (dyskeratosis congenita) and ribosomal function (Schwachman–Diamond syndrome) [3,4]. Acquired AA is usually the result of an autoimmune attack that appears to be directed at hematopoietic stem/progenitor cells [5–7]. The objective of this article is to summarize the current literature on treatment strategies in acquired AA and to discuss promising approaches in the management of patients with severe AA.



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**Financial & competing interests disclosure** The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.
No writing assistance was utilized in the production of this manuscript.

## Diagnosis of acquired aplastic anemia

Acquired AA can occasionally be traced to a distinct trigger such as seronegative hepatitis, drugs, toxins or pregnancy, but the vast majority of cases are classified as idiopathic. Clinical manifestations are proportional to the peripheral blood cytopenias and may include dyspnea on exertion, fatigue, easy bruising, petechiae, epistaxis, gingival bleeding, heavy menses, headache and fever. A complete blood count, leukocyte differential, reticulocyte count and a bone marrow aspirate and biopsy can establish the diagnosis. Peripheral blood flow cytometry to detect cells missing glyco sylphosphatidylinositol anchored proteins (GPI-AP) [8–10], bone marrow karyotyping and FISH to help exclude hypoplastic myelo dysplastic syndromes (hMDS) should be performed on all patients. GPI-AP deficiency is a hallmark of paroxysmal nocturnal hemoglobinuria (PNH); however, small-to-moderate populations of GPI-AP deficient cells (usually 0.1–15%) can be found in most patients with acquired AA at diagnosis [11]. Finding a PNH clone in patients with AA can be helpful in excluding congenital forms of the disease.

A hypocellular bone marrow biopsy is required for the diagnosis of AA. Spicules from an aspirate may be surprisingly cellular in some patients despite overall marrow hypo cellularity as most patients will have residual pockets of ongoing hematopoiesis. Thus, a 1–2 cm core biopsy is essential for assessing cellularity. Mild dyserythropoiesis is not uncommon in AA, especially in cases with simultaneous small-to-moderate sized PNH populations; however, the presence of a small percentage of myeloid blasts or dysplastic features in the myeloid or megakaryocyte lineages favors a diagnosis of hMDS [12,13]. Distinguishing between AA and hMDS is often challenging, especially in older patients. The percentage of $CD34^+$ cells in the bone marrow is often helpful [12]. The percentage of $CD34^+$ cells is usually <0.3% in AA, whereas the $CD34^+$ percentage is either normal (0.5–1.0%) or elevated in hMDS. Blood from the initial aspirate should be tested for chromosomal abnormalities via cytogenetics and FISH. Abnormal cytogenetic studies at the time of diagnosis may suggest an alternative diagnosis, it may be an independent predictor of poor response to immunosuppressive therapy and may be associated with a higher cumulative leukemic transformation rate [14].

Aplastic anemia is classified as non-severe (NSAA), severe (SAA) and very severe based on the degree of the peripheral blood cytopenias (Box 1). The 2-year mortality rate with supportive care alone for patients with SAA or very severe AA approaches 80% [6], with invasive fungal infections and overwhelming bacterial sepsis being the most frequent causes of death. The clinical course of NSAA is quite variable, it is seldom life-threatening and in many instances requires no therapy [15]. In a recent review of 96 NSAA patients in Korea from 1997–2007, 41.7% of the patients were initially asymptomatic. A total of 62 patients were treated with oxymetholone, anti-thymocyte globulin and cyclosporine, cyclosporine alone or other agents after initial diagnosis. During the follow-up period, 18 patients progressed to SAA and the median progression time was 18 months. Initial white blood cell count and absolute neutrophil count in the evolution group tended to be lower than in the group that did not progress. A total of 16 patients showed overall improvement, whereas three patients developed secondary hematologic disease, acute myeloid leukemia (AML), myelodysplastic syndrome (MDS) and PNH. Their data suggest that low pretreatment levels of white blood cells and absolute neutrophils are associated with progression to more severe disease. Furthermore, patients with thrombocytopenia that did not respond to treatment with immunosuppression had a higher frequency of progression (33%) to SAA [16].

## Initial supportive care

Before initiating more definitive therapies for acquired SAA, the clinician must consider the significant supportive care required for these patients. An individual patient's requirement for supportive care will depend upon the severity of symptoms and pancytopenia.

### Transfusions

Patients with severe cytopenias require urgent support with blood products. Blood products should be irradiated to prevent transfusion associated graft-versus-host disease (GVHD) [17,18], and filtered to reduce the incidence of viral infections and prevent alloimmunization [19]. Transfusions from family members should be avoided to decrease sensitization to potential bone marrow donors. The initial goal of transfusion therapy for anemia should be to correct or avoid cardiopulmonary complications. Most patients without significant comorbidities should be transfused with packed red blood cells when symptomatic. The goal of platelet transfusion should be to maintain a high enough platelet count to prevent spontaneous bleeding. For most patients, platelet transfusions are indicated when platelet levels are below 10,000/ul or if the patient is experiencing bleeding. Granulocyte transfusions remain controversial in AA and should be used judiciously. A recent study of granulocyte infusions in patients with SAA showed a potential role in patients with severe bacterial or fungal infections. A retrospective analysis was performed on all patients with SAA who had received granulocyte transfusions between 1997 and 2007 in a single institution. Infections in the study patients were both invasive bacterial and fungal infections unresponsive to maximal antibiotic and/or anti fungal therapy. The overall survival (OS) to hospital discharge was 58%. Survival was strongly correlated with hematopoietic recovery. The mean post-transfusion absolute neutrophil count did not differ significantly in either the responders or nonresponders. The data suggest that granulocyte transfusions may have an adjunctive role in severe infections in patients with SAA [20].

### Growth factors

The use of HGFs to support blood counts is of limited value in SAA, as predicted by both *in vitro* studies and measurement of endogenous serum levels of HGF, which are markedly elevated. There may be a limited role for granulocyte colony stimulating factor (G-CSF) administration in an attempt to stimulate a neutrophil response in the presence of severe infection, although there have been no prospective randomized studies showing a benefit for G-CSF in SAA patients [21]. In France, a randomized multicenter study was conducted to evaluate the efficacy and safety of G-CSF during the first 12 weeks of standard immunosuppressive therapy (IST) in 102 patients with untreated SAA. At a median followup of 5 years, no difference was observed between the group who received G-CSF and those who did not in terms of survival, hematological response and occurrence of secondary leukemias (one patient in each group). These data suggest that G-CSF support with IST might be used for patients with SAA as it significantly enhances neutrophil recovery but it must be recognized that it does not modify the overall response and survival [22]. Another randomized multicenter study of over 100 previously untreated patients with SAA in Japan also demonstrated no survival benefit of G-CSF with IST. Two secondary leukemias were also reported in this trial [23]. A systematic review and meta-analysis of data from the Annual Meeting of the American Society of Hematology (2002–2007), the European Group for Blood & Marrow Transplantation (EBMT; 2002–2008), the Annual Meeting of the European Hematology Association (2002–2007) and the Annual Meeting of the Society for Hematology and Stem Cells (2002–2007) demonstrated that treatment with growth factors (erythropoietin or G-CSF) does not affect mortality rate or improve complete and overall hematologic response. Likewise, growth factors do not alter the occurrence of refractory disease, the rate of clinically documented or severe infections, but are associated

with a decreased risk of relapse [24]. There are also data suggesting that HGFs may have a deleterious effect in SAA. In a retrospective survey among 840 patients with SAA registered by the EBMT who received immunosuppressive therapy with or without G-CSF, a small but significant increase in hazard (1.9) of AML/MDS was reported in the G-CSF-treated group [25,26].

## Infections

Fungal and bacterial infections are a major cause of death in patients with SAA. Data from children suggest that mortality from fungal infections is higher in patients with SAA than in patients with AML or acute lymphoblastic leukemia [27]. However, an active fungal infection should not delay more definitive therapy such as IST or bone marrow transplant (BMT) [28]. In contrast to the high incidence of aspergillus infections, *Pneumocystis jiroveci* infections are rare among patients with SAA, given that T cells are not defective [29]. Patients with SAA are at risk for all types of infections including Gram-positive as well as Gram-negative infections [30]. There is no standardized approach to antibiotic therapy in these patients. A recent case report suggests that continuous-infusion β-lactam antibiotics are a potentially useful treatment strategy for resistant *Pseudomonas aeruginosa* infections in immunocompromised patients [31]. Patients are also susceptible to viral infections, particularly community-acquired respiratory viruses, members of the *Herpesviridae* family and the viral hepatitides. Vigilance and proactive prescription of prophylactic antibiotics (when deemed clinically appropriate), antivirals and antifungals in this patient population is imperative [29].

## Definitive treatment

**Hematopoietic stem-cell transplantation—**Bone marrow transplantation is potentially curative and is the treatment of choice for children and young adults (age of <30 years) with SAA who have an HLA-matched sibling donor. An advantage of BMT over standard IST is a marked reduction both in the risk of relapse and the evolution of late clonal disorders such as MDS and PNH [32]. A recent report from the EBMT of over 1500 patients confirmed that predictors of survival following BMT included matched sibling donor, age of less than 16 years, early transplant (time from diagnosis to transplant of less than 83 days) and a non-radiation conditioning regimen [33]. Most patients achieve full donor chimerism after BMT; however, early and late graft rejection with persistent pancytopenia may occur. Patients with a progressive increase in host cells >5%, especially around the time of withdrawal of immuno suppressive therapy, appear to have the greatest risk of late graft failure. Graft rejection is a greater obstacle for unrelated transplants. The rate of late graft failure is lower in patients who achieve full donor chimerism by 1 year or those patients with stable mixed chimerism (<5% host) at 1 year. This observation suggests a benefit of serial assessment of donor chimerism prior to withdrawing IST [34]. Interestingly, graft failure is not always deleterious in acquired SAA since autologous recovery may occur following cyclophosphamide (CY)-based condition therapy [35,36]. A recent retrospective ana lysis of 1024 consecutive patients in the AA Working Party of the EBMT showed a cumulative incidence of autologous recovery at 4.2% (95% CI: 3.1–5.6%). OS at 10 years was 84% for patients demonstrating host recovery, 74% for engrafted patients, and just 16% for non-engrafted patients who did not experience autologous reconstitution of hemato poiesis [37]. The EBMT reviewed outcomes in nearly 700 patients with SAA receiving transplants from HLA-matched siblings. A total of 134 grafts were peripheral blood progenitor cell grafts, and 558 were bone marrow grafts. In patients older than 20 years of age, chronic GVHD and overall mortality rates were similar after both types of transplantations. In patients younger than 20 years of age, rates of chronic GVHD (relative risk 2.82; $p = 0.002$) and overall mortality (relative risk 2.04; $p = 0.024$) were higher after transplantation of peripheral blood progenitor cell grafts than after transplantation of bone marrow. In younger patients, the 5-

year OS was 85% after BMTs but only 73% after peripheral blood progenitor cell grafts. These data suggest that bone marrow grafts are preferable in young patients undergoing HLA-matched sibling donor transplantation for SAA [38].

**Conditioning—**Cyclophosphamide (50 mg/kg/day × 4 days) with or without anti-thymocyte globulin (ATG), is commonly used for conditioning before BMT in patients with SAA. Although this regimen is non-myeloablative, the immunosuppression is sufficient to allow engraftment in most cases [39–41]. Avoidance of total body irradiation (TBI) and busulfan markedly reduces transplant-related complications such as mucositis, GVHD, second malignancies and infertility. Survival rates following matched sibling allogeneic BMT have steadily improved since the 1970s largely because of improved supportive care, especially in the area of GVHD prophylaxis [40]. A recent randomized controlled study of CY with and without ATG demonstrated that graft failure and GVHD were similar, and the addition of ATG did not improve OS [42]. Fludarabine (FLU) has been added to CY conditioning in SAA patients in an attempt to decrease graft failure and improve OS. In a small cohort of young patients (median age 20 years), 38 patients were treated; 24 were treatment naive, 11 had failed previous IST and three had failed hematopoietic stem-cell transplantation previously. The FLU/CY regimen was well tolerated with minimal transplant-related mortality. Engraftment was observed in all patients. The median time for engraftment of neutrophils and platelets was 18 and 23 days, respectively. Graft rejection with a relapse of aplasia was observed in one patient. The OS at 43 months post-transplant was 79% [43]. Larger studies are necessary to determine what role FLU and CY will have as our transplant experience continues. The use of FLU-based regimens has enabled engraftment in heavily transfused and sometimes alloimmunized patients [44].

## Choice of donor: HLA-matched siblings or alternative donors

Fewer than 30% of patients will have an HLA-matched sibling donor. Unfortunately, unrelated donors and mismatched transplants have almost twice the transplant-related mortality and risk of GVHD as matched sibling donor transplants [45]. Thus, BMT from unrelated or mismatched donors is usually reserved for patients who fail to respond to one or more courses of IST. Among patients who do receive unrelated or mismatched transplants, the best results are seen in patients under the age of 21 years with disease duration of less than 1 year [45–47]. The International Bone Marrow Transplant Registry reported on the results of 318 alternative donor transplants in patients with SAA between 1988 and 1998 [48]. Most patients in this series were young, heavily transfused and of poor performance status. The probability of graft failure was 20% and the survival probability at 5 years was less than 40%. The Fred Hutchinson Cancer Research Center (Seattle, WA, USA) reported on the results of unrelated allogeneic BMT in SAA after conditioning with low-dose TBI, high-dose CY and ATG [49]. The median age was 19 years, and with a median follow-up of 7 years, 61% of HLA-identical and 40% of HLA nonidentical transplant recipients survived the procedure; however, more than 70% of patients acquired acute GVHD and over 50% developed chronic GVHD. A recent meta-ana lysis of 18 heterogeneous trials evaluated the outcomes for patients who received unrelated donor transplants after failure to respond to IST. This suggests that a stable performance status and detailed HLA-matching contribute to improved survival [50]. A review of data from the EBMT was performed to determine further outcomes for patients receiving BMT from an unrelated donor for SAA. They analyzed 498 patients transplanted during 1990–2005. Survival at 5 years increased from 32±8% before 1998 to 57±8% after 1998 ($p < 0.0001$). After 1998, there was less graft failure (11 vs 26%; $p < 0.0001$), less acute GVHD (cumulative incidence 28 vs 37%; $p = 0.02$) and less chronic GVHD (22 vs 38%; $p = 0.004$). The authors suggest that these improvements in outcomes are due to better donor matching [51]. A more recent ana lysis from the EBMT-SAA working party retrospectively reviewed the outcome of 100 patients

undergoing an alternative donor transplant, after IST had failed. All patients received a combination of FLU, CY and ATG with or without low dose (2 Gy) TBI as conditioning. The actuarial 5-year survival was 73% for the group that received FLU, CY and ATG (FCA) and 79% for the group given the conditioning regimen including TBI. The most significant predictor of survival was the interval between diagnosis and transplantation, with 5-year survival rates of 87 and 55% for patients grafted within 2 years of diagnosis and more than 2 years after diagnosis, respectively ($p = 0.0004$). The overall cumulative incidence of acute GVHD grades II–IV and III–IV was 18 and 7%, respectively, with no difference between the two regimens. Chronic GVHD was recorded in 27% of the FCA group and 50% of the FCA-TBI group ($p = 0.06$). This study confirms that outcomes are improving for SAA patients undergoing alternative donor transplants [52].

## GVHD prophylaxis

A major cause of morbidity and mortality for patients undergoing BMT, especially in older patients and in alternative donor transplants, is GVHD. The most commonly used GVHD prophylaxis is a calcineurin inhibitor such as tacrolimus or cyclosporine A (CsA) [53]. The combination of methotrexate (MTX) and CsA (MTX-CsA), as well as the combination of mycophenolate mofetil (MMF) and CsA (MMF-CsA) have been successfully used for GVHD prophylaxis. In a recent prospective trial of 47 patients, MMF-CsA (compared with MTX-CsA for acute GVHD prophylaxis) showed equivalent rates of OS and event-free survival at 2 years [54]. Research into GVHD prophylaxis for unrelated donor transplantation is also ongoing. A retrospective comparative ana lysis using 47 matched pairs, of tacrolimus/MTX and CsA/MTX showed improved 5-year OS in the tacrolimus group (82.8%) compared with 49.5% in the CsA group ($p = 0.0124$) [55]. Interest has recently turned towards high-dose CY as GVHD prophylaxis. Investigators from Johns Hopkins (MD, USA) have demonstrated in mice that high-dose post-transplantation CY facilitates partially HLA-mismatched hematopoietic stem-cell transplantation without severe GVHD [56] and can mitigate, if not completely nullify, the negative impact of HLA-disparity on transplantation outcome. High-dose CY is also effective as single agent, short-course prophylaxis of GVHD after nonmyelo ablative conditioning and HLA-matched allogeneic-BMT in humans [57]. Recently, this same group reported successful use of high-dose post-transplantation CY as GVHD prophylaxis in two patients with refractory SAA; both patients were over 50 years of age and neither developed GVHD [58].

## Immunosuppressive therapy

**Compared with BMT—**Another highly effective therapy for SAA is ATG and CsA IST and is generally first-line therapy for SAA patients who lack matched sibling donors or are not good candidates for BMT. The hematopoietic response rate after ATG/CsA is 60–70% and the probability of survival at 5 years ranges from 60 to 85% [59,60]. However, up to 40% of patients eventually relapse [60]. In a recent outcomes study from the EBMT of 2479 patients with SAA, actuarial survival analyses were performed according to whether the patient's first-line treatment was BMT or IST. At 10 years the survival was 73% in BMT recipients and 68% in those treated with IST ($p = 0.002$). The rates of secondary malignancy were tenfold higher in the patients who received IST alone (1.2%) compared with those who received BMT (0.1%) [60,61].

**IST for NSAA—**There is only one prospective randomized trial of CsA alone or the combination of ATG/CsA treatments in patients with NSAA. In this study the end point was the hematologic response at 6 months. A significantly higher overall response rate of 74% was found in the ATG and CsA group, with 57% complete and 17% partial responders ($p = 0.02$). Compared with CsA alone, the combination of ATG and CsA resulted in a significantly higher median hemoglobin level and platelet count at 6 months. The survival

probabilities for the two groups were comparable at 93% for the CsA group and 91% for the ATG/CsA group [62].

**IST for SAA—**In patients with SAA, there is a prospective randomized trial of the addition of sirolimus to the combination of ATG/CsA in which this agent did not improve the response rates for these patients [63].

Tacrolimus as an alternative to CsA has been investigated in children with SAA and found to have comparable responses rates (88 vs 85%) with a more favorable side effect profile [64].

Additional immunosuppressive drugs such as MMF have been added to the ATG/CsA combination with the aim of decreasing relapse and secondary clonal disease. However, as yet no improvement in response of relapse rates has been observed when compared with the standard ATG/CsA [65]. PNH may also arise following IST for SAA. A recent retrospective ana lysis was performed for PNH clones measured by flow cytometry in over 200 consecutive SAA patients who received IST from 2000–2008. In the 60% of patients without a detectable clone pretreatment, the appearance of a clone after IST occurred at least once in 21% of the patients but persisted in only 10%. However, in 30 patients, an increase in clone size was observed after IST. The majority of these patients did not require specific interventions with anticoagulation and/or eculizumab over a follow-up period of just 24 months. Of the seven patients who did require therapy for clinical PNH symptoms and signs, all had an elevated lactate dehydrogenase and a clone size greater than 50%. Of the patients who did have a detectable clone at diagnosis, only ten patients lost this clone after IST. The remaining 73 patients with a clone at diagnosis experienced a gradual decrease in the PNH clone size, noted in the months following IST [66].

**IST in older patients—**The outcomes for tolerability and toxicity, response and relapse rates were examined in 24 older patients (over 60 years of age) receiving IST. Seven patients received standard IST consisting of standard-dose ATG with or without CsA, and 17 patients received attenuated IST consisting of at least a 50% dose reduction of ATG with CsA or CsA alone. Six patients (25%) had early deaths, mostly due to infection. Early mortality appeared higher in the standard IST group, although this was not statistically significant (43 vs 18%; $p = 0.4$). The 2-year cumulative incidence of response was 42% (95% CI: 26–69%). Responders had significantly better survival than non responders ($p = 0.0002$). The 3-year probability of OS was 49% (95% CI: 27–68%). Nine out of 14 evaluable patients in the attenuated IST group had durable responses to treatment. These data from this small cohort suggest that attenuated dose IST could be a reasonable treatment option for patients deemed unfit for standard-dose IST [67].

There are currently no standard criteria to deem IST a treatment failure. Many institutions use 4 months of IST without response to deem that treatment was ineffective before moving to a secondary treatment. Prognostication for response to IST is an ongoing area of research. It is known that telomere mutations and shortening can be found in bone marrow failure syndromes such as dyskeratosis congenita [68]. The determination of telomere length is useful for the characterization of many bone marrow failure disorders, including SAA, by the quantitative (q)PCR method [69]. Interest in determination of the clinical significance of short telomeres in SAA prompted an ana lysis of 183 patients at the National Heart Lung and Blood Institute (MD, USA). All patients had pretreatment measurements of telomere length and were subsequently enrolled into immunosuppression protocols. The authors concluded from their results that there was no relationship between hematologic response and telomere length with response rates to IST. Multivariate analyses did demonstrate that shorter telomere length was associated with relapse, clonal evolution and mortality. OS for

the quartile with shortest telomeres was 66% (95% CI: 52.9–82.5%) surviving 6 years whereas the remaining, longer telomere patients had an OS of 83.8% (95% CI: 77.3–90.9%). Those with the shortest telomere length also had a higher likelihood of progressing to monosomy 7 [70].

## High-dose CY

Considering the rates of relapse and secondary clonal disease following ATG/CsA [71–73], a need for better nontransplant approaches persists. Reports of autologous hematopoietic reconstitution with durable remissions in SAA patients after allogeneic BMT following high-dose CY conditioning suggest that high-dose CY alone is capable of treating the disease [74–76]. In 1976, a case report in the *New England Journal of Medicine* described a patient with AA successfully treated with high-dose CY without BMT [77]. The first published series of high-dose CY therapy for SAA was published in 1996 [74]. This pilot study included just ten patients, but durable complete remissions were achieved by seven patients. One of the complete responders died from acquired immunodeficiency syndrome 44 months after treatment with high-dose CY. The six remaining patients are alive and in continuous complete remission, with a median follow-up of 10.8 years (range: 7.3–17.8 years) at the time of publication. Enthusiasm for the high-dose CY approach was tempered by a randomized controlled trial at the NIH comparing high-dose CY/CsA with ATG/CsA. The study was terminated after enroll- ing just 31 patients over a period of 3 years because of greater toxicity in the CY/CsA arm, despite the fact that none of the stopping rules or primary or secondary end points were reached. Only 13 patients in the CY/CsA arm and 12 patients in the ATG/CsA arm were evaluable at 6 months. The 6-month mortality in the CY plus CsA arm (three out of 13 patients) was not significantly different from the mortality in the ATG arm (one out of 12 patients; $p = 0.3\%$). No actuarial data or data beyond 6 months were presented. However, the report did document five relapses and one case of MDS in the ATG arm, compared with just one relapse in the CY arm. Although the study clearly shows slower hematopoietic recovery and greater need for blood products and antibiotics in the CY/CsA arm, the other end points of the study (response rate, response duration, OS and evolution to secondary clonal disease) were not evaluated [78]. The Johns Hopkins group recently updated their experience of high-dose CY in 67 additional patients with SAA [76]; 44 of these patients had not received prior IST (treatment naive) and 23 had previously received one or more immunosuppressive regimens (refractory). The trial also employed the use of G-CSF. At 10 years, the overall actuarial survival was 88%, the response rate was 71%, with the majority being complete, and the actuarial event-free survival (where death, relapse, MDS, BMT and PNH requiring treatment are defined as events) was 58% in 44 treatment naive SAA patients (Figure 1). Patients with refractory SAA fared less well after high-dose CY therapy; at 10 years, overall actuarial survival, response and actuarial event-free survival rates were 62, 48 and 27%, respectively. For treatment-naive patients, the median time to a neutrophil count of $0.5 \times 10^9$/l was 60 days (range: 28–104) and the median time to last platelet transfusion was 117 days (range: 24–640 days). The median time to a neutrophil count of $0.5 \times 10^9$/l was 54 days (range: 35–119 days) and the median time to last platelet transfusion was 103 days (range: 51–751 days) for patients with refractory SAA. The median time to complete remission was 20 months (range: 4–70 days). The data demonstrate that high-dose CY is an effective and potentially curative therapy for patients with treatment-naive SAA. Early deaths secondary to invasive fungal infection are no higher after high-dose CY than those reported after ATG/CsA. Relapse and secondary clonal disease may occur in a minority of patients, but approximately 60% of patients achieve durable hematopoietic recovery and do not require further immunosuppressive agents. High-dose CY is less effective for patients with refractory SAA, but durable responses occur in approximately a quarter of these patients.

## Expert commentary

With modern therapies, the 5-year survival rate for SAA exceeds 85%. BMT offers the best chance for cure, but its use is restricted by the relatively high morbidity and mortality, especially in older patients and those who lack an HLA-matched sibling donor. IST remains the standard of care and leads to meaningful remissions in up to 75% of patients, but the high rate of relapse and secondary clonal diseases makes this therapy less attractive, especially for young patients with SAA. Unfortunately, the addition of newer IST (e.g., MMF and sirolimus among others) to ATG/CsA does not seem to improve response or decrease the risk of relapse or clonal disease. High-dose CY therapy seems to produce higher quality remissions with fewer relapses, but this has not been confirmed in randomized controlled trials. For first-line therapy, patients should be made aware of the greater experience with IST when choosing between IST and high-dose CY for first-line therapy. Although supportive care has greatly improved with antifungal therapy, we seem to have reached a plateau in the effectiveness of IST. Therefore, in order to improve outcomes for patients with SAA, there is a need for either improved IST that results in fewer relapses or less toxic BMT therapies that mitigate graft failure and GVHD, especially when using alternative donors.

## Five-year view

Currently, advances in mitigating graft failure and GVHD in the setting of alternative donor BMT appear to be outpacing the development of more effective IST therapies for SAA. Over the next 5 years there is likely to be great use of unrelated and HLA-mismatched BMT to treat SAA, especially in patients who do not respond or relapse after IST. The development of post-transplant CY to expand the donor pool and mitigate GVHD is especially promising.

## Acknowledgments

This work was supported, in part, by grants from the NIH: P01 CA70970 (Robert A Brodsky) and 5K12 HL087169-05 (Amy E DeZern).

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**Box 1**

Aplastic anemia: definitions and diagnosis

**Severe AA**

- Any two of three required for diagnosis
  - – Absolute neutrophil count <500/$mm^3$
  - – Platelets <20,000/$mm^3$
  - – Reticulocyte count <1.0% corrected or <60,000/$mm^3$

**Very severe AA**

- Meets criteria for severe disease and absolute neutrophil count <200/$mm^3$

**Non-severe AA**

- Does not meet criteria for severe AA

AA: Aplastic anemia.

Key issues

- Ensuring that alternative diagnoses have been eliminated prior to beginning therapy for severe anaplastic anemia is important.
- In children and young adults, it is important to rule out congenital bone marrow failure syndromes.
- In older adults, alternative causes of the bone marrow failure syndrome can be hypoplastic myelodysplastic syndrome and paroxysmal nocturnal hemoglobinuria. It is also important to distinguish between them.
- It is crucial to initiate early supportive care in severe anaplastic anemia.
- It is important to use irradiated blood products and avoid transfusions from potential bone marrow donors.
- Early consideration of bone marrow transplantation in younger patients with a matched sibling donor is a significant part of the therapeutic process.
- If a patient is not a suitable bone marrow transplant candidate, the physician should use immunosuppressive therapies such as anti-thymocyte globulin/ cyclosporine A or high-dose cyclophosphamide.

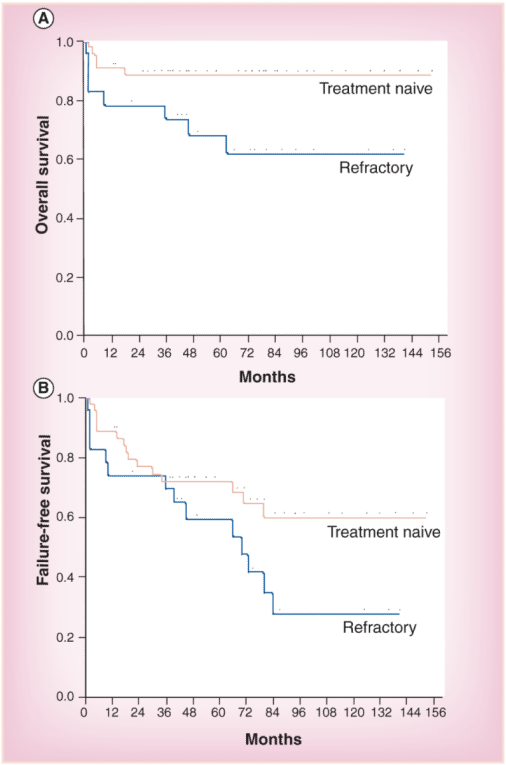


**Figure 1. Results of high-dose cyclophosphamide therapy for severe aplastic anemia**

**(A)** Overall survival after high-dose cyclophosphamide therapy for 44 treatment-naive patients (upper line) and 23 patients refractory to prior immunosuppressive therapy (lower line), p = 0.03 (log rank test). **(B)** Failure-free survival after high-dose cyclophosphamide therapy for 44 treatment-naive patients (upper line) and 23 patients refractory to prior immunosuppressive therapy (lower line), p = 0.07 (log rank test). This research was originally published in [76]. © The American Society of Hematology.