

## \* CHAPTER 33

# HSCT for aplastic anaemia in adults

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## 1. Introduction

Acquired aplastic anaemia (AA) is a life-threatening disorder characterised by bicytopenia or pancytopenia in the peripheral blood and an aplastic/hypoplastic bone marrow. AA is considered severe if marrow production is inadequate in at least 2 cell lines and as very severe if the neutrophil count is  $<0.2 \times 10^9/L$ , because of the high risk of infection. The patho-physiology of AA is heterogeneous. Features include a reduced pool of haematopoietic progenitor cells, accelerated apoptosis in haematopoietic progenitor cells, immunemediated suppression of haematopoiesis, clonal abnormalities and telomere shortening in progenitor cells (1, 2).

Differential diagnosis includes congenital bone marrow failure syndromes, some of which may manifest late, i.e. in early adulthood, and hypoplastic MDS. It is often wise to repeat the diagnostic marrow studies to exclude aplastic crisis due to a drug or an infection. Clonal aberrations on cytogenetic studies and dysplastic erythropoietic islands do not exclude SAA, but marrow fibrosis, the presence of blast cells, and dysplastic myelo- or megakaryopoiesis are arguments in favour of a hypoplastic MDS. Once the diagnosis is established treatment is by bone marrow transplantation (BMT) or immunosuppressive therapy (IS). In HSCT for AA the use of bone marrow rather than PB is recommended.

## 2. Treatment

Treatment goals are to improve peripheral blood counts to achieve transfusion independence and to avoid infection risks. The outcome of SAA patients has improved considerably over time both after BMT and IS. The 5-year survival for patients reported to the Registry of the EBMT SAA Working Party is 70–80% both after immunosuppressive treatment and after HLA-identical sibling BMT (Figure 1). The choice of the primary treatment is based on availability of an HLA-identical sibling, patient age (Figure 2) and disease severity. The EBMT compared outcome after BMT and IS using a stratified proportional hazard model to estimate effects of age and neutrophil count on failure-free survival in both treatment groups (3). Table 1 presents the estimated differences in 5-year failure-free survival between the 2 initial treatment options as a function of age and neutrophil count. Negative values indicate a survival disadvantage of BMT compared with IS, while positive values indicate a survival advantage for BMT. This allows the identification of 3 groups of patients:

1. Patients in whom BMT is superior, including children regardless of neutrophil count and adults up to the age of 40 with low neutrophil counts ( $\leq 0.3 \times 10^9/L$ );
2. Patients in whom IS is superior, comprising adults above age 40;
3. Patients in whom no differences were found (3).

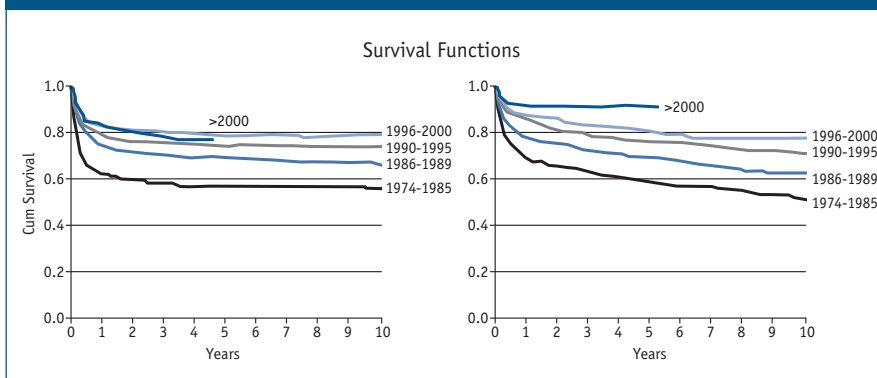
The difference in projected survival between patients treated with BMT and IS is

**Table 1: Differences between BMT and IS in 5-year failure free survival (%) after initial treatment (3)**

Neutrophil count (x 10 <sup>9</sup> /L)	Age (Y)				
	10	20	30	40	50
0	24*	20	14	6	-2
0.1	19	14	8	1	-7
0.2	14	9	3	-4	-11
0.3	10	5	-1	-7	-14
0.4	6	1	-4	-10	-16
0.5	3	-2	-7	-12	-17**

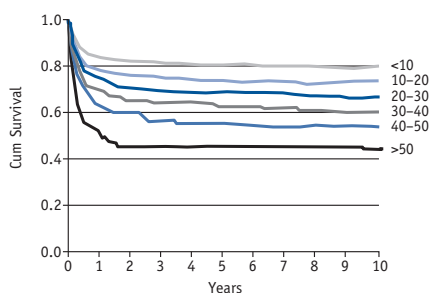
Positive values: Advantage for BMT (\*24% 5-yr failure free survival difference in favour of BMT)

Negative values: Advantage for immunosuppression (\*\*17% difference in favour of immunosuppression)

**Figure 1: Survival after HLA-identical stem cell transplantation (1a) or immunosuppression (1b) as first line treatment stratified by year of treatment**

not linear but increases with time in favour of BMT. This may be explained by more early deaths with BMT, mainly due to GvHD and more late events (clonal complications and relapse) in patients treated with IS. This view has been recently challenged by studies indicating that children even with very severe disease may have excellent outcome when treated with IS, even better than patients without very severe disease (4). This may be due to improved supportive care with fewer infectious deaths possibly supporting patients long enough to benefit from treatment.

**Figure 2: Patients receiving BMT by age, 0–10 years, 10–20, 20–30, 30–40, 40–50 and older than 50 with youngest patients having best survival and oldest patients having poorest survival**



### 3. Results: Stem cell transplantation

#### 3.1. Conditioning for HLA-identical sibling transplantation

The standard preparative regimen in HLA-identical sibling transplantation for non-sensitised patients is cyclophosphamide at a dose of 200 mg/kg b.w. (4x50 mg/kg on days -5 to -2) with or without anti-thymocyte globulin (ATG) (5).

In a non-randomised trial a combination of cyclophosphamide + ATG resulted in lower incidence of chronic GvHD and improved survival compared with historical controls who received cyclophosphamide alone (6, 7). However, a prospective randomised trial in 131 patients did not detect a significant benefit from the addition of ATG to cyclophosphamide as a preparative regimen for patients with severe AA (8).

Irradiation-based conditioning is generally not recommended for sibling donor transplantation. While irradiation-based regimens have been effective in reducing rejection, they have accomplished this goal at the price of increased transplant-related complications (9–11). There are however interesting data in unrelated donor transplantation with the addition of 2Gy of TBI to reduce the graft failure rate (12).

#### 3.2. Stem cell source

The use of peripheral blood stem cells (PBSC) as a stem cell source alternative to BM for allogeneic transplantation is increasing for all indications. A number of studies have shown that PBSC is associated with higher risks of chronic GvHD and in patients with advanced malignancy in an increased graft versus leukaemia effect.

In a joint EBMT/IBMTR retrospective analysis results of 151 HLA-identical sibling PB HSCT were compared with results of 722 HLA-identical sibling BMT for AA. Other than faster haematopoietic recovery, this study shows a higher incidence of chronic GvHD and lower survival for HSCT with PB, especially in young patients (13). Currently half the transplants reported to the EBMT for SAA use peripheral blood as a stem cell source in spite of the recommendation to use marrow as a stem cell source.

### **3.3. Post-transplant immunosuppression in HLA-identical sibling transplantation**

The introduction of cyclosporin A (CsA) in the 1980s resulted in decreased transplant-related mortality, significantly reduced rejection rates and improved survival (14). In a prospective randomised trial comparing CsA + methotrexate (MTX) with CsA alone, the 1-y TRM rates for patients given CsA/MTX or CsA alone were 3 and 15%, respectively (15). The 5-year probability of survival was 94% in the CsA/MTX group and 78% for those in the CsA alone group. Even though these differences appear large if attributed to the addition of MTX alone, the current recommendation is to use CsA + MTX as post-transplant immunosuppression.

### **3.4. Alternative donor transplantation**

In the past, survival after alternative donor transplantation has been poor (16). Therefore it was only considered as salvage therapy for patients failing to respond to one or more courses of IS. The optimum conditioning therapy and post-transplant immunosuppression for alternative donor BMT in AA has yet to be established. Approaches currently under investigation are addition of fludarabine or radiotherapy and ATG to the standard combinations. Promising data are reported from a GITMO/EBMT AA WP trial with a survival probability of 82% in AA patients conditioned with a combination of low-dose cyclophosphamide, ATG, fludarabine and CsA + MTX as GvHD prophylaxis (17). It is also important to consider risk factors for the alternative donor BMT in AA: a fully matched donor for both Class I and Class II by high-resolution typing and early transplantation provides better results. A recent study by the EBMT using observational data shows improvement in outcome with long-term survival for patients receiving unrelated donor transplants from 32% (+8%) before 1998 to 57% (+8%),  $p < 0.0001$  in those transplanted after 1998. This improvement was associated with less graft failure, less acute and chronic GvHD and fewer infectious deaths, probably due to better donor selection and possibly progress in antimicrobial treatment (18).

There is very limited information on the use of haploidentical donors and the series using cord blood as a stem cell source are too small at this time for meaningful comparisons.

#### 4. Results: Immunosuppressive treatment

A combination of ATG, CsA and corticosteroids represents the current standard as first-line immunosuppressive therapy both for severe and non-severe AA (19–21). Response rates with this regimen are in the order of 65 to 75% (at 4–6 months). There is little agreement on the duration of immunosuppressive treatment and some experts recommend withdrawing CsA after 6 months whereas others treat for a longer period. Relapse in responding patients is not uncommon (30–40%), but can be retreated effectively in the majority of patients. Patients not responding to 2 cycles of ATG are unlikely to respond to additional treatment. Late complications include PNH and MDS. MDS is seen in 5–10% of patients after IS; whether incidence is linked to growth factor administration is unknown (22). Data supporting such an association in observational studies need confirmation by prospective trials. Pilot studies of G-CSF in combination with ATG + CsA have reported encouraging results with respect to early mortality, trilineage response and survival. A randomised trial confirmed improved neutrophil recovery but no advantage in terms of overall response and survival by addition of IS (23). A large EBMT multicentre randomised trial comparing ATG + CsA versus ATG + CsA + G-CSF has recently been completed and the results are awaited. The most commonly used ATG preparation in Europe, equine ATG (Lymphoglobulin), has recently been withdrawn from the market. Whether the rabbit product by the same manufacturer (Thymoglobulin), using a similar manufacturing procedure (stimulation with human thymocytes) is equivalent remains to be determined. A recent study by a Chinese group comparing different types of ATG with or without CsA and growth factors showed that not all ATG preparations are equivalent (24). There is little experience with other immunosuppressive agents. Studies are ongoing using Campath in patients refractory to ATG + CsA. The EBMT collects data not only on transplant patients but also on nontransplant treatments. This has allowed for multiple studies comparing outcomes with different treatment strategies (Table 1). Long-term survival with immunosuppressive treatment has continuously improved over the last years (Figure 1). This improvement is most likely due to improved supportive care, as the main drugs used to treat the disease (ATG and CsA) have not changed over the years.

#### 5. Discussion and future perspectives

Treatment of SAA has greatly improved the outcome of these patients over the past 30 years. Unresolved issues are: chronic GvHD in transplant recipients, transplantation for older patients not responding to immunosuppressive treatment, transplantation using alternative donors, the use of growth factors with immunosuppressive treatment and patients refractory to immunosuppressive treatment without an adequate donor.

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## Mutiple Choice Questionnaire

To find the correct answer, go to <http://www.esh.org/ebmt-handbook2008answers.htm>

### 1. The best standard immunosuppressive treatment for severe aplastic anaemia is:

- a) Anti-lymphocyte globulin .....
- b) Anti-thymocyte globulin + mycophenolate .....
- c) Anti-thymocyte globulin + cyclosporin .....
- d) High dose cyclophosphamide .....

### 2. Which characteristic is frequently found in aplastic anaemia?

- a) Splenomegaly .....
- b) Marrow fibrosis .....
- c) A positive PNH test .....
- d) Increased marrow blasts .....

### 3. The main factor(s) affecting mortality when it comes to decide between transplant or immunosuppression as a first line treatment is/are:

- a) Donor CMV status and platelet transfusion needs .....
- b) Patient age and neutrophil count .....
- c) Donor sex and a positive PNH test .....
- d) Availability of an unrelated donor .....

### 4. Which of the following statements is true in aplastic anaemia?

- a) Peripheral blood is the best stem cell source because of faster neutrophil engraftment .....
- b) Marrow is the best stem cell source because of it causes less chronic GvHD .....
- c) Peripheral blood is the best stem cell source because it is easier to harvest from the donor .....
- d) Marrow is the best stem cell source because stromal cells accelerate engraftment .....

**5. To transplant a patient with aplastic anaemia from a sibling donor the best established conditioning regimen is:**

- a) i.v. busulfan and cyclophosphamide .....
- b) 12 Gy of total body irradiation and cyclophosphamide .....
- c) Cyclophosphamide and anti-thymocyte globulin .....
- d) Melphalan and fludarabine .....