

# New Advances in the Treatment of Acquired Severe Aplastic Anaemia

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## Abstract

Severe acquired aplastic anaemia (ASAA) is now a treatable, often curable disease. Without specific therapy the probability of survival at 3 years is only 20-30%. The Severe Aplastic Anaemia Working Party of the European Group for Blood and Marrow Transplantation has set up a unique registry of 4634 patients treated throughout Europe from 1974-2001. The Registry includes patients treated by immunosuppressive therapy (IST) and by allogeneic stem cell transplantation (SCT), and has been a valuable tool for investigating the outcome of treatment and for facilitating the design of prospective randomised studies.

When a HLA identical sibling donor is available SCT should be carried out as soon as possible to reduce the probability of death from infection. Early transplantation reduces the probability of mortality from graft failure or bleeding through an alloimmune response to blood products. The use of limited field or total body irradiation in the pre-transplant conditioning protocol is detrimental as there is an increased probability of graft versus host disease and endocrine failure. Irradiation is also associated with a higher probability of late transplant related malignancy. It remains controversial whether the inclusion of anti-thymocyte globulin (ATG) in the pre-transplant conditioning improves survival compared with high dose cyclophosphamide alone. A well documented improvement in survival has been attributed to inclusion of cyclosporin (CyA) in the post graft immunosuppressive regimen and to improvements in supportive care. In the 1998-2001 cohort the probability of 3 year survival is 83%, 77% and 30% for patients aged  $\leq 16$ , 17-40 and  $> 40$  years respectively.

The results of IST have also improved steadily over the past 25 years. The addition of CyA to a 5 day course of ATG was shown to improve survival in a prospective randomised study by the German group. The addition of CyA and improvements in supportive care have been the main factors in the improved survival of children and adults treated for ASAA with IST. In the 1998-2001 cohort the 3 year probability of survival after IST is 85%, however there is a 10-15% probability of clonal progression of disease at 10 years in the survivors. Clonal evolution to paroxysmal nocturnal haemoglobinuria, MDS and AML are all documented. IST is well tolerated and older patients without significant co-morbidity aged 65-75 can be considered for treatment. Currently the Working Party is undertaking a prospective randomised study to test the effect of adding G-CSF to ATG and CyA in the experimental arm of the study.

Young patients who are non responders to IST after 240 days are considered for HLA 'matched' unrelated donor SCT. Pilot studies using fludarabine containing protocols without total body irradiation have been responsible for recent improvements in survival. However results remain significantly worse than for HLA identical sibling transplants. For older patients who fail immunosuppressive treatment the outlook is poor. Pilot studies using alternative immunosuppressive agents are being undertaken.

In summary, The treatment of choice for young patients with an HLA identical sibling remains SCT with the intention of cure. In contrast all new patient with ASAA without a HLA identical sibling donor, those over 35-45 years of age and those with non-severe aplastic anaemia should be treated with IST as first line therapy.

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