

Recent advances in the treatment of severe aplastic anemia

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Primary treatment The outcome of patients with AA has improved considerably over time after both stem cell transplantation and immunosuppressive treatment. The estimated 3-year survival for patients reported to the registry of the EBMT Aplastic Anaemia Working Party (EBMT AA WP) was 85% after immunosuppressive treatment and 73% after HLA-identical stem cell transplantation.

The choice of the primary treatment should be based on availability of an HLA-identical sibling, the age of the patient and the severity of the disease.

Transplantation. The standard preparative regimen in HLA-identical sibling transplantation for un-sensitized patients is cyclophosphamide at a dose of 200 mg/kg b.w. (4x50 mg/kg on days -5 to -2). Irradiation-based conditioning should be avoided. While radiation-based programs have been effective in reducing rejection, they have accomplished this goal at the price of increased transplant-related complications, especially second tumours. In a non-randomized trial a combination of cyclophosphamide + antithymocyte globulin (ATG) resulted in lower incidence of chronic GvHD and improved survival compared with historical controls who received cyclophosphamide alone. However, a prospective randomized 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.

Stem cell source The use of peripheral blood stem cells (PBSC) as alternative stem cell source to BM for allogeneic transplantation is increasing. Whereas a lot of information on the outcome after PBSCT compared with BMT is now available from controlled clinical trials and large retrospective studies for a number of malignant hematologic

diseases, the relative efficacy of these two approaches for non-malignant disorders like AA is unknown. In a joint EBMT/IBMTR retrospective analysis results of 151 HLA-identical sibling PBSCTs were compared with results of 722 HLA-identical sibling BMTs for AA. Other than early hemopoietic recovery, this study suggests no advantage of PBSCT over BM for HLA-identical sibling transplants for AA and raises concerns about possibly poorer long-term outcome with PBSCT. Transplantation of PBSCT should be discouraged in AA patients.

Post-transplant immunosuppression in HLA-identical sibling transplantation .The inclusion of cyclosporine A in the transplant protocol was associated with decreased transplant-related mortality, significantly reduced rejection rates and improved survival.. In a prospective randomized 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%. The 5-year probability of survival was 94% in the CsA/MTX group and 78% for those in the CsA alone group.

Alternative donor transplantation The optimum conditioning therapy and post-transplant immunosuppression for 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 65% in 38 acquired AA patients conditioned with a combination of low-dose cyclophosphamide, ATG, fludarabine and CsA/MTX as GvHD prophylaxis.

Immunosuppressive Treatment. A combination of antithymocyte globulin (ATG), CsA and corticosteroids represents the current gold

standard as first-line immunosuppressive therapy both for severe and non-severe AA. Response rates with this regimen are in the order of 65% to 75% (at 4-6 months). The addition of G-CSF to the combination ATG/CsA produces encouraging results, although a randomized trial has shown no advantage in terms of overall response and survival for patients receiving growth factor. GITMO has completed a randomized comparing 5 μ g/kg vs 10 μ g/kg in addition to ATG/CsA, and has confirmed the predictive role of white blood cell increments on outcome, but no advantage of using a larger dose of G-CSF. An EBMT multicenter randomized trial, comparing ATG/CsA versus ATG/CsA/G-CSF, is now ongoing (see homepage of the AA WP at www.ebmt.org for details).

Conclusions. Survival of patients with AA has improved substantially over the last two decades both after BMT and IS. In the last years we also observe improved outcome after alternative donor SCT. Standards of treatment have been established. Appropriate choice of the first-line treatment and early treatment without undue delay in experienced centres is important.

Abbreviations: EBMT= European group for blood and marrow transplantation; GITMO= gruppo italiano trapianti di midollo osseo; WPSAA= working party aplastic anemia; ATG= anti-thymocyte globulin; CsA= cyclosporin A.