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CONSENSUS STATEMENT

BLOOD AND MARROW STEM CELL TRANSPLANTS IN AUTOIMMUNE DISEASE

A consensus report written on behalf of the European League Against Rheumatism (EULAR) and the European Group for Blood and Marrow Transplantation (EBMT)

A. TYNDALL and A. GRATWOHL

Department of Rheumatology and Division of Hematology, Department of Internal Medicine, Kantonsspital Basel, Switzerland

THE First International Symposium on Haemopoietic Stem Cell Therapy in Autoimmune Diseases took place in Basel on September 26–28, 1996. This 2-day-long meeting gathered around 250 people (30 were invited speakers or chairmen) of whom about half were involved in rheumatology/immunology and the other half in haematology/oncology.

This document has been prepared by members of the Scientific Committee and was the basis of the discussion in open forum on September 28, 1996.

BACKGROUND

The current concept views autoimmune disease (AD) as a consequence of disturbed and altered immune response leading to an attack by the immune system against host antigens. The reaction is polyclonal and contains B- and T-cell components. The basic mechanisms are still poorly understood. However, once established, the disease process usually continues and leads to tissue destruction and sometimes death.

All cells of the immune system are derived from the haemopoietic stem cell. As in the case of the monoclonal origin of haematological malignancies, it is unknown whether the true stem cell itself is affected or only its progeny. Experimental data in animals clearly show that some diseases can be cured by allogeneic transplants from healthy, non-affected, major histocompatibility complex-compatible donors and also by autologous transplants.

CLINICAL EVIDENCE

Allogeneic transplants

There is clinical evidence that allogeneic bone marrow transplantation (BMT) can lead to long-lasting remission and eventually cure. The greatest experience is available in severe aplastic anaemia which is considered, at least in part, as an autoimmune disease. Most transplants were performed on patients with an autoimmune disease and concomitant or underlying haematological disorder, e.g. gold-induced severe aplastic anaemia in patients with rheumatoid arthritis or autoimmune diseases in patients with leukaemia. A single case of relapse of rheumatoid arthritis following allogeneic BMT has been reported where the immune cells were of donor origin. The major risk of allogeneic BMT is the occurrence of graft-versus-host disease and its associated risk of mortality.

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Autologous transplants

Present patient data are still anecdotal, heterogeneous and with a limited follow-up. They show that sufficient stem cells can be collected to repopulate the haemopoietic system following ablative therapy when techniques are used as in the treatment of haematological malignancies. It is too early to know whether in autoimmune diseases toxicity is different or whether long-lasting remissions can be obtained.

The following recommendations can be made based on available data.

General. In patients with a disorder such as leukaemia which would normally be treated with BMT, the presence of a concomitant AD should not be considered as a contraindication to BMT, but rather a potential added bonus. In the absence of haematological disorders, blood and marrow transplantation in autoimmune disease should be viewed as an experimental procedure to be carried out only after informed consent of the patient, after consultation by two independent experts in the field and according to a protocol approved by the institutional review board or a research ethics committee. Data reporting should be an integral part of the treatment protocol.

Donor type. Syngeneic (identical twin) transplants would be ideal treatment if an unaffected donor is available (rare).

Autologous BMT is in general preferred due to its safety profile (3–5% mortality) and current experience. Age limit 65 yr.

Allogeneic sibling donor transplants can be considered if an HLA-identical sibling donor is available and if the risks of disease exceed the risks involved in an allogeneic transplant (15–35% mortality). Since transplant-related mortality increases with age, patients should be considered for an allogeneic blood or marrow transplant up to the age of 55 yr. Until the benefits of the procedure are more clearly defined, unrelated volunteer donor transplants are not recommended.

Disease indication. In principle, only diseases severe enough to have an increased risk of mortality should be considered. Transplants should be undertaken before irreversible organ damage has taken place such that significant clinical benefit can be achieved.

Rheumatological disorders
1. Systemic sclerosis (scleroderma).
2. Autoimmune pulmonary hypertension (after adequate trial of immunosuppression).
3. Necrotizing vasculitis (following induction with standard immunosuppression).
4. Rheumatoid arthritis (RA) with severe complications e.g. necrotizing vasculitis, scleritis.
5. RA, poor prognosis, rapidly progressive and destructive, resistant to adequate treatment—Bu/Cy regimen preferred in RA. (Bu is radiomimetic and possibly more effective against memory cells.) Cy alone not excluded.
6. Systemic lupus erythematosus (SLE)—major organ threat, failed conventional therapy.
7. Antiphospholipid antibody syndrome.
8. Severe, uncontrollable cryoglobulinaemia.
9. Paediatric rheumatology:
   systemic sclerosis variants with pulmonary fibrosis;
   severe dermatomyositis (especially with pulmonary fibrosis);
   severe necrotizing vasculitis.
   NOT juvenile arthritis at this stage.

Neurological disorders
1. Multiple sclerosis—conditioning with either:
   a. drugs which cross the blood/brain barrier (e.g. busulphan) or
   b. total body irradiation (TBI) (caution is necessary since in rats with experimental allergic encephalomyelitis (EAE) exacerbations are seen. Glucocorticoid cover may be of benefit in humans).
2. Myasthenia gravis.

Haematological diseases (not discussed in detail)
1. Severe refractory autoimmune thrombopenia.
2. Autoimmune haemolytic anaemia.
3. Immune neutropenia.
4. Combinations thereof.

Other conditions for consideration (not discussed in detail)
1. Inflammatory bowel disease, e.g. Crohn's.
2. Autoimmune diabetes mellitus.

Source of transplant. Theoretically, marrow or peripheral blood stem cells can be used. Since it has been clearly documented that autologous peripheral blood stem cells lead to a faster and more complete recovery, peripheral blood stem cells are preferred to bone marrow-derived stem cells for autologous transplants. However, bone marrow-derived stem cells contain fewer mature autoreactive T cells which may prove to be important if purging techniques fail to remove enough such cells. More data are required on this issue.

Mobilization of stem cells for autologous transplants. Available data do not suggest that results of mobilization with haematological growth factors in patients with autoimmune diseases are different from those of mobilization in patients with haematological malignancies or solid tumours.

Standardized approaches involve mobilization with G-CSF alone at a dose of 10 μg/kg/day s.c. once daily or following a priming dose of cyclophosphamide 4 g/m^2 once.

Mobilization and stem cell collection should only be performed by approved haemato-oncological teams experienced in the collection of haemopoietic stem cells. The target cell dose for reinfusion should be $\geqslant 2 \times 10^6$ CD34-positive cells/kg or $> 2 \times 10^4$ CFU-GM/kg. If manipulation *ex vivo* is planned, $> 3 \times 10^6$ CD34-positive cells will need to be harvested.

Manipulation of the graft. Autoimmune diseases have both B- and T-cell components, and it is possible that T or B cells in the graft contribute to relapse of the disease and failure of the blood and marrow transplant, as they do in haematological malignancies. Animal data suggest that this could be the case, as do some early anecdotal human case reports. Therefore, T-cell purging is recommended aiming to transplant $< 1 \times 10^5$ cells/kg body weight of cells. If T or B cells are removed, the number of transplant CD34-positive cells, T and B cells, as well as the methods employed, should be recorded.

Conditioning for the transplant. Ablation of the diseased immune system is the goal of the conditioning regimen. Animal data suggest that inclusion of TBI might have an advantage. However, TBI (and radiomimetic drugs) is associated with an increased risk of late malignancies in patients with severe aplastic anaemia. There are no data to prove that any particular conditioning regimen has a special advantage in AD. For a comparative analysis of single cases, four conditioning regimens, all traditionally used in blood or marrow transplants, are suggested.

(a) Cyclophosphamide 50 mg/kg for 4 days as a 1 h i.v. infusion from days −5 to −2 before the transplant, as is standard treatment for aplastic anaemia. Antithymocyte globulin may or may not be added.
(b) Cyclophosphamide 60 mg/kg for 2 days at 1 h i.v. infusion followed by TBI as currently used at the treating centre.
(c) Busulphan 16 mg/kg orally over 4 days in 16 doses of 1 mg/kg each followed by cyclophosphamide 60 mg/kg at 1 h infusion for 2 days. Anti-convulsant prophylaxis is required.
(d) Combination chemotherapy BEAM (BCNU 300 mg/m^2 i.v. day −7, VP-16 250 mg/m^2 i.v. daily × 2 doses day −7 to day −4, Ara-C 200 mg/m^2 daily × 2 doses day −7, −6, −4, melphalan 140 mg/m^2 i.v. day −3).

The use of novel conditioning regimens for autoimmune diseases at this early stage is discouraged, since it may increase the difficulty in assessing the results of treatment.

Trial planning. At this stage of development, clearly designed phase I and II pilot trials are the main objective. Whenever possible, they should follow a standardized protocol.

Several research ethics committee-approved protocols exist for systemic sclerosis (autologous with and without TBI and allogeneic) and autoimmune pulmonary hypertension. Clinicians should be encouraged to adhere at least to the core components of these protocols concerning mobilization, conditioning and graft product manipulation.

Data reporting. Scientific analysis and evaluation of new techniques are an integral part of treatment. All patients, once mobilization has been initiated, should be reported to the EBMT-EULAR Autoimmune Disease Data Registry regardless of clinical outcome. Consecutive patients should be reported.

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Contributors to the consensus discussion included: B. Adams, B. Ansell, F. Appelbaum, P. A. Bacon, C. M. Black, F. C. Breedveld, P. Brooks, G. R. Burmester, M. Elliott, P. Emery, H. Euler, A. Fassas, S. Foreman, D. Fürst, E. Gluckman, J. M. Goldman, N. C. Gorin, A. Gratwohl, G. R. V. Hughes, J. Kalden, R. Krance, A. M. Marmont, F. Melchers, R. Mertelsmann, H. H. Peter, H. G. Prentice, T. Rolink, G. Rosti, S. A. Schey, N. Schmitz, S. Slavin, J. Smolen, K. M. Sullivan, A. Tyndall, D. W. van Bekkum, F. G. A. van de Meché, L. B. A. van de Putte, T. L. Vischer.