Review

Immune ablation and stem-cell therapy in autoimmune disease Clinical experience

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Abstract

In the past 5 years, around 350 patients have received haematopoietic stem cell (HSC) transplantation for an autoimmune disease, with 275 of these registered in an international data base in Basel under the auspices of the European League Against Rheumatism (EULAR) and the European Group for Blood and Marrow Transplantation (EBMT). Most patients had either a progressive form of multiple sclerosis (MS; $n = 88$) or scleroderma (now called systemic sclerosis; $n = 55$). Other diseases were rheumatoid arthritis (RA $n = 40$), juvenile idiopathic arthritis (JIA; $n = 30$), systemic lupus erythematosus (SLE; $n = 20$), idiopathic thrombocytopenic purpura (ITP; $n = 7$) and others. The procedure-related mortality was around 9%, with between-disease differences, being higher in systemic sclerosis and JIA and lower in RA (one death only). Benefit has been seen in around two-thirds of cases. No one regimen was clearly superior to another, with a trend toward more infectious complications with more intense regimens. Prospective, controlled randomized trials are indicated and being planned.

Keywords: autoimmune disease, bone marrow transplantation, stem cell

Introduction

Five years ago the concept of haematoimmunoablation with HSC rescue was forwarded as a possible treatment for severe autoimmune disease, and a statement was published before the first patient underwent the procedure [1•]. As of April 2000, around 350 patients had been so treated. Thus, sufficient experience has been accumulated to state that, in selected cases, an acceptable risk–benefit ratio exists to justify the commencement of prospective, comparative randomized trials to determine the place, if any, of such an expensive and toxic procedure in the treatment of autoimmune disease.

The combination of improved bone marrow transplantation (BMT) techniques, now called HSC transplantation, supportive animal data [2] and coincidental observations (ie improvement in coexisting autoimmune disease after HSC transplantation for conventional indications, such as aplastic anaemia, leukaemia and cancer [3]) has allowed the concept to move forward to the clinic.

Haematopoietic stem-cell transplantation

HSCs that are capable of replenishing the whole haematopoietic and immune system can be obtained from peripheral blood rather than from direct marrow aspiration.

BMT = bone marrow transplantation; EULAR/EBMT = European League Against Rheumatism/European Group for Blood and Marrow Transplantation; HSC = haematopoietic stem cell; IBMTR = International Bone Marrow Transplant Registry; ITP = idiopathic thrombocytopenic purpura; JIA = juvenile idiopathic arthritis; MS = multiple sclerosis; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus; SSc = systemic sclerosis; TRM = transplant-related mortality.

This process of driving the usually scanty HSCs out of the bone marrow is called mobilization or priming, and is achieved with high doses of cytotoxic drugs and/or with growth factors.

Once the HSCs have been mobilized to peripheral blood, leucopheresis, usually about 2 weeks after mobilization, is performed to harvest the leucocytes. These leucocytes are now rich in stem cells, and they are either cryopreserved directly or further manipulated to enrich for HSCs, such as CD34 selection, and then stored. This is called graft manipulation or purging, and may include other steps to remove unwanted cells, such as B or T cells.

With sufficient CD34 cells collected to ensure engraftment ($>2 \times 10^6$/kg recipient body weight), the patient returns about 1 month later for the conditioning (haematoimmunoablation) with cytotoxic drugs with or without radiation therapy. If antithymocyte globulin is used at this stage, its action is considered more as *in vivo* purging of T cells, rather than conditioning. The graft is then returned to the patient, and in around 10–12 days enough red cells, neutrophils and platelets are being produced to allow cessation of support therapy (transfusions of red cells and platelets, growth factors and antimicrobial agents).

The recovery of the immune system is more delayed, with a vast amount of published information available concerning the recovery first of natural killer cells and B cells, followed by $CD8^+$, and later by $CD4^+$ cells [4••].

A transplant-related mortality (TRM) of under 3% is often quoted for autologous HSC transplantation, although this only applies to adjuvant treatment for solid tumours. For lymphoma and leukaemia, around 10% is more realistic. For allogeneic HSC transplantation, a TRM of 15–35% is seen, the difference being due to more complex immunological reactions leading to graft rejection and graft-versus-host disease, which are not often seen in autologous HSC transplantation. Early results from the EULAR/EBMT database for autoimmune disease [5•] suggest a TRM of approximately 8–9%, perhaps relating to a sicker population of patients with involvement of vital organs, such as heart and lungs.

Patient selection

From the beginning it was decided that only those patients in whom a significant risk to life or to vital organs existed, and who had failed a trial of 'best available' conventional therapy should be treated [6••]. In addition, the patients should be able to enjoy a reasonable quality of life if the autoimmune process were arrested, and not be extensively damaged by irreversible pathology, such as fibrosis. It was also considered critical that the clinical state of the patient at the time of transplant should not be so poor so as to select for high morbidity and mortality without benefit.

Table 1

Registration in the EBMT/EULAR database (April 2000)

Disease	*n*
MS	88
Myasthenia gravis	1
SSc	55
SLE	20
RA	40
Juvenile chronic arthritis	30
Mixed connective tissue disease	3
Dermatomyositis	4
Wegener's granulomatosis	3
Cryoglobulinaemia	3
ITP	7
Pure red cell aplasia	4
Autoimmune haemolytic anaemia	2
Evans' syndrome	1
Thrombotic thrombocytopenic purpura	1
Other	3

Data from the EBMT/EULAR database.

Data on 275 reports (270 autologous, five allogeneic) from 64 transplant centres from 20 countries have now been registered in the EULAR/EBMT database in Basel, Switzerland (Table 1). This has allowed a more precise definition of inclusion and exclusion criteria that are based on experience rather than theoretical considerations alone (Table 2). Criteria for other diseases such as systemic lupus erythematosus and dermatomyositis/polymyositis are still evolving.

In addition, around 50 cases have been registered in the Milwaukee-based International Bone Marrow Transplant Registry (IBMTR), and nearly 50 unregistered case reports have been published, totalling around 350 patients with autoimmune disease who have been treated with HSC transplantation.

Treatment regimens and protocols

Most patients have been treated in the context of a phase 1/2 pilot study, consistent with the published guidelines (Table 3). The majority of patients with MS received mobilization with cycloposphamide and granulocyte colony-stimulating factor, followed by conditioning with BEAM and antithymocyte globulin, and grafting with a $CD4^+$ selected product.

There is no suggestion that one or other regimen is superior for any autoimmune disease group, although there appears to be more procedure-related morbidity/mortality

Table 2

Inclusion criteria for HCS transplantation in various autoimmune diseases

Disease/ general principles	Criteria
General	Failed best available conventional therapy Progressive disease, poor prognosis (for life or organ) Reasonable quality of life if autoimmune disease activity were arrested <60 years old Able to withstand HSC transplantation (especially cyclophosphamide 4 g/m^2)
SSc	Diffuse skin disease for <3 years and progressive plus other organ involvement Modified Rodnan >16 (max 51) Diffuse skin disease for >3 years or limited skin and vital organ involvement (threatening) Mean PAP <50 mmHg, DLCO >45% predicted LVEF >50% of normal (on echo), >45% MUGA Controlled arrhythmias Hypertension controlled by ACE inhibitors Serum creatinine <1.5 times normal upper limit
RA	Failed: two DMARDS (including methotrexate) + any combination of DMARDS + anti-TNF regimen Progressive destruction Disease duration 2–10 years
MS	Disease duration ≥1 year EDSS between 3.0 and 6.5 Disability progression sustained for at least 6 months during the previous 2 years of: ≥1.5 EDSS points if entry EDSS between 3.0 and 5.0 ≥1.0 EDSS point if entry EDSS ≥5.5 Primary or secondary progressive MS Clinical or MRI activity during the past year

ACE, angiotensin-converting enzyme; DLCO, lung diffusion capacity; DMARD, disease-modifying antirheumatic drug; EDSS, extended disability score system; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; MUGA, multigated image acquisition; PAP, pulmonary artery pressure; TNF, tumour necrosis factor.

Table 3

Guidelines for conditioning regimens before HSC transplantation

Cyclophosphamide 50 mg/kg for 4 days at a 1-h infusion from days –5 to –2 before the transplantation; this is standard treatment for aplastic anaemia. Antithymocyte globulin may or may not be added

Cyclosphamide 60 mg/kg for 2 days at 1-h infusion followed by total body irradiation, as currently used at the treating centre

Busulfan 16 mg/kg orally over 4 days in 16 doses of 1 mg/kg each, followed by cyclophosphamide 60 mg/kg a 1-h infusion for 2 days; anticonvulsant prophylaxis is required

Combination chemotherapy: BEAM (BCNU 300 mg/m^2 intravenously day –7; VP-16 250 mg/m^2 per day, divided over two doses each day, from days –7 to –4; Ara-C 200 mg/m^2 per day, divided over two doses each day, on days –7, –6 and –4; melphalan 140 mg/m^2 intravenously on day –3)

Table 4

Causes of death after HSC transplantation

	Causes of death		
Disease	Progressive disease	Toxicity	Infection
MS	1	2	5
SSc	4	8	1
RA	0	–	1
JIA	1	1	4
SLE	–	1	1
ITP			
Amytrophic lateral sclerosis	1	–	–

with the more ablative regimens and severe T-cell depleting protocols. Some protocols have been revised as a result, such as introducing lung shielding in a systemic sclerosis (SSc) protocol, which included total body irradiation, due to two possible radiation-related pulmonary deaths (McSweeney P, personal communication).

Toxicity

Although as yet there have been no fatal outcomes published in the literature as case reports, the EULAR/EBMT database shows a TRM of approximately 9% [5•]. This includes mobilization-associated mortality, an event that is not usually reported to traditional BMT databases. The causes of death were as seen previously with HSC transplantation (ie infection, bleeding and organ toxicity), with a tendency to occur more in certain disease subgroups such as SSc and JIA, systemic form (Table 4). However, no disease subgroup has been spared from fatal outcomes.

It is suspected that this may be due to a poorer clinical state of such patients at the time of mobilization and/or transplant, especially relating to cardiopulmonary and other vital organ involvement, which is in contrast to MS and RA patients. It is considered possible that a macrophage activation syndrome could have been responsible for some of the JIA fatal cases. Protocols have been amended accordingly. These amendments include stricter exclusion criteria for the following: SSc, including mean pulmonary artery pressure greater than 50 mmHg; and JIA, including avoiding transplant during periods of high systemic activity, avoiding severe T cell depletion below 2×10^5/kg body weight and the use of pulse intravenous methylprednisone during granulocyte colony-stimulating factor support therapy (Wulffraat N, personal communication). Although these modifications are logical, there is no hard data to confirm that they will reduce procedure-related mortality.

Table 5

Clinical response HSC transplantation

	Disease				
Clinical response	MS	SSc	RA	JIA	SLE
Evaluated	75	33	35	25	14
Better	24	21	14	16	10
Stable	27	3	2	1	0
Better than progressed	7	7	13	7	3
Worse	17	2	6	1	1

Values are number of patients in each category.

Clinical outcome

Table 5 shows the outcome as reported to the EULAR/EBMT database using the traditional BMT form of complete remission, partial remission, no response and death. Follow-up data includes those available after 3 months after transplant or mobilization, and is incomplete. Further autoimmune disease subgroup analysis is underway, with more extensive clinical data in MS, SSc, RA/JIA and SLE.

However, using these and other published data, some statements are possible at this stage. In SSc, an impact on skin score of greater than 25% improvement in nearly 70% of patients has been observed (Binks M, manuscript submitted), and in MS improvement or stabilization of both primary and secondary forms has been observed in 78% [7], using the extended disability score system. In RA, approximately 50% relapse rates have been seen [8•] (although most authors report that the synovitis after transplant is easier to control than beforehand), with similar observations in JIA. In RA, T-cell depletion did not seem to reduce the relapse rates [9].

In RA, there have been some other issues that complicate the current trial planning and data interpretation. The introduction of antitumour necrosis factor-α in the past year in some countries reduced the number of 'failed best available therapy' patients considerably. In addition, although full and sustained remission is unusual in RA, there is little data to suggest that an allogeneic approach would necessarily be more effective.

Future directions

Some issues are similar to the experience so far with HSC transplantation for other conditions such as leukaemia and solid tumour. The major one of these is the need for prospective, randomized comparative trials to confirm the impressions gained from phase 1 (safety) and phase 2 (efficacy) pilot studies.

There are examples where first impressions, either optimistic or pessimistic, were not confirmed by such trials, although many investigators had already formed an 'opinion', on the basis of their own small experience, and were therefore reluctant afterwards to randomize patients. Autologous HSC transplantation in breast cancer is a good example of this.

After many meetings of involved parties, such trial designs for MS, SSc and JIA have been generated, with the intension to extend them as multicentre studies, given the relatively low incidence of these autoimmune diseases. Outlines of these protocols are available from Basel on e-mail (alan.tyndall@fps-basel.ch), and will soon be posted on the EBMT Internet page for autoimmune disease (http://gildor.conexis.es/ebmt). RA trial design is still under discussion.

Other issues are more specific to autoimmune disease, and therefore require an open-minded approach. For example, growth factors for mobilization may induce a flare of autoimmune disease, and this has been observed in JIA, MS and RA, at times possibly contributing to a fatal outcome. It is logical but not proven that cyclophosphamide given 8 days before granulocyte colony-stimulating factor could reduce such an effect, and this has been included in the second-generation study designs.

Also, cyclophosphamide 4 g/m^2 for mobilization could induce a long-lasting remission of autoimmune disease, without the need to proceed to myeloablation, and this could be a point of randomization in some protocols (eg in SLE or RA). One report in RA [10] supports this concept. In some autoimmune diseases, cyclophosphamide may be more cardiotoxic than usual, as suggested in SSc, and alternatives may be needed for mobilizing and conditioning.

The question regarding whether allografts should be performed, especially the newer nonmyeloablative 'minigraft', has been raised if relapse rate is too high after autologous HSC transplantation. In our opinion, the point at which this option should be considered has not yet been reached, and the superiority of allo-HSC transplantation has not been proven in autoimmune disease. The risk of TRM is already higher than initially anticipated in autoimmune disease, and it is possible that this risk in allo-HSC transplantation, with its attendant risk for graft-versus-host disease, could also be higher, despite sibling fully matched donors.

Data collection

Complete collection of standardized transplant and disease-specific data is essential if we are to fairly judge and compare what has been achieved. After 2 years of intense international collaboration, involving EULAR, American College of Rheumatology, EBMT, IBMTR, US

National Institutes of Health, and neurological and other specialty groups, there are now such core data forms for the major autoimmune disease subgroups of MS, SSc, RA, JIA and SLE. These data are available from either Basel (www.ebmt.org for non-American cases) or the IBMTR (ibmtr@mcw.edu for all American registrations), and will be integrated into BMT registries worldwide throughout 2000.

An international meeting will take place in Basel, October 5–7, 2000, to review all the data and plan trials (www.akm.ch/stemcell2000).

Inevitably, any such core data set must be a compromise between enough (for outcome research) and not too much (to ensure that the forms are filled out fully). A revision is planned after 12 months' experience.

Conclusion

There are sufficient data to justify proceeding to prospective, randomized comparative trials of HSC transplantation in the treatment of severe autoimmune disease. The basic principle of therapeutic advantage should be established first, before 'fine tuning' of protocol details are tested.

Given the relative rarity of suitable cases, the expense and risk of the procedures and the potential heterogeneity of protocols, international multicentre trials should be undertaken to avoid duplication of effort. This should ensure that a minimum amount of time is devoted to determining the role of this potentially life-saving procedure in selected cases, or avoid unnecessarily exposing others to its risks.

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