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Stem cell transplantation: a treatment option for severe systemic sclerosis?

J M van Laar,¹ D Farge,² A Tyndall³

ABSTRACT

High-dose immnosuppressive therapy and autologous stem cell transplantation (commonly referred to as "stem cell transplantation") is an established treatment for a variety of haemato-oncological conditions. Recent studies have confirmed its potent clinical and immunological effects in rheumatic autoimmune diseases, including severe diffuse systemic sclerosis (SSc). With modifications of treatment protocols and more stringent selection of patients, the safety profile of stem cell transplantation has improved as expressed in lower treatment-related morbidity and mortality. Prospective, randomised trials are in progress in Europe and North America to compare the safety and efficacy of stem cell transplantation with conventional chemotherapy in patients with early diffuse SSc, on the premise that induction of remission in early disease can be achieved by stem cell transplantation as a means to interrupt fibrogenesis.

Systemic sclerosis (SSc) is a complex connective tissue disease characterised by clinical and laboratory features of vasculopathy, fibrosis, inflammation and autoimmunity. Two subsets can be identified—limited and diffuse SSc. Quality of life and functional ability in most patients are impaired owing to Raynaud’s disease, skin thickening and contractures. Patients with the diffuse subset and organ involvement, in particular, are at high risk of early mortality, with 5-year survival rates comparable with patients with lymphoma.

While the aetiology of SSc is unknown, significant progress has been made in elucidating some of the pathogenetic mechanisms involved in SSc (reviewed by Denton and Black⁴). Skin specimens from patients with early SSc contain monoclonal inflammatory infiltrates, whereas those of patients with advanced disease tend to be more fibrotic. This observation and experimental studies are in keeping with the hypothesis that fibroblasts are activated by (autoactive?) T and B lymphocytes, leading to formation of myofibroblasts and excessive matrix production in skin and internal organs. Vascular symptoms due to vasculopathy universally precede the other manifestations of SSc and it is thought that the repetitive or persistent local release of oxygen radicals is a key event in the transformation of the stromal cell compartment. Cross talk between cells is in part mediated by cytokines, some of which are dysregulated in SSc—for example, interleukin (IL)6, IL4, transforming growth factor (TGF)β.

A recent study on CTGF polymorphism underlined the role of genetic factors (and cytokines) in the predisposition to develop SSc.⁵ Nevertheless, treatment with an anti-TGFβ monoclonal antibody was ineffective in a controlled, double-blind study.⁶ Of all other treatments investigated in SSc so far, only cyclophosphamide-based regimens have shown a consistent, but modest, benefit on skin thickening and lung involvement, waning after discontinuation of treatment.⁷ No treatment has proved to be effective in improving long-term outcome, as testament to the huge unmet need in this disease. In part, this may be attributed to inclusion in trials of patients with end-stage SSc, not amenable to disease-modifying treatment. For example, serial lung function studies in patients with SSc have shown that the greatest decline in lung function occurs in the first 4 years.⁸ Based on these and other available clinical data, early SSc could provide a brief opportunity to evaluate the disease-modifying properties of new treatments.

Stem cell transplantation (SCT) is the short name for a multistep treatment aimed at resetting of the immune system by high-dose immnosuppressive treatment (HDIT) combined with SCT. Its introduction in the field of autoimmune disease in the mid-1990s built on extensive experience in haemato-oncology of treating malignant diseases with (non)myeloablative conditioning and autologous or allogeneic bone marrow transplantation. Early pioneering work by the Seattle transplant team had shown that a small proportion of patients with leukaemia survived after allogeneic bone marrow transplantation, showing its curative potential.⁹ With better selection of patients and adaptations of transplant protocols, treatment-related toxicity and mortality was reduced and long-term survival improved. Treatment-related mortality of autologous and allogeneic stem cell transplantation generally is below 5% and 15%, respectively, for most indications now.

The therapeutic potential of HDIT + SCT in autoimmune disease was first seen in patients with rheumatoid arthritis (RA) treated with allogeneic bone marrow transplantation for gold-induced aplastic anaemia. These clinical observations were corroborated by studies in several animal models of experimental autoimmune disease (reviewed by Van Bekkum). The models were instrumental in identifying the optimal transplant regimen to induce remission. Although these conditions differed slightly between disease models, the principle that HDIT + SCT can cure autoimmune disease was firmly established. Of note, autologous SCT proved as effective as allogeneic SCT in some models, thus paving the way for its application in human autoimmune disease.

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Box 1 End points of the ASTIS trial

Primary end points
The primary end point of the ASTIS-trial is event-free survival. Event-free survival is defined as the time in days from the day of randomisation until the occurrence of death due to any cause or the development of persistent major organ failure (heart, lung, kidney) defined as follows:

- Heart: left ventricular ejection fraction <30% by multigated radionuclide angiography (MUGA) (or cardiac echo);
- Lungs: respiratory failure—that is, resting arterial oxygen tension (PaO₂) <8 kPa (<60 mm Hg) or resting arterial carbon dioxide tension (PaCO₂) >6.7 kPa (>50 mm Hg), or both, without oxygen supply;
- Kidney: need for renal replacement therapy.

Secondary end points
The major secondary end points of the study are treatment-related mortality, treatment toxicity and progression-free survival, defined as the time in days since the day of randomisation until any of the following changes from baseline has been documented at two consecutive 3-month evaluations:

- death,
- 10% drop in (forced) vital capacity or ≥15% drop in carbon monoxide transfer factor (of predicted values), or both,
- 15% drop in left ventricular ejection fraction by echo or MUGA,
- 15% drop in body weight,
- 30% drop in creatinine clearance,
- 30% increase in skin score,
- 0.5 increase in Scleroderma Health Assessment Questionnaire.

European Blood and Marrow Transplant/European League Against Rheumatism (EBMT/EULAR), which issued guidelines for patient eligibility criteria and transplant protocols and set up a registry to collect data from transplanted cases in Europe. A subsequent retrospective analysis of registry data from 473 patients and data from a number of pilot studies confirmed the feasibility of SCT in autoimmune diseases. Interestingly, the probability of disease progression, overall survival and treatment-related mortality appeared dependent on conditioning intensity and underlying disease, with the highest survival and lowest treatment-related mortality in RA and lowest survival and highest treatment-related mortality in SSc and systemic lupus erythematosus (SLE), probably reflecting their severity and extent of internal organ involvement. With time and experience, the risks of HSCT have decreased significantly, as illustrated by the gradual drop in transplant-related mortality from 17% in the first cohort of 41 patients with SSc from the (EBMT/EULAR) registry to 8.7% in a subsequent analysis of 65 patients (which included the first four cohort patients). To overcome the limitations of registry analyses, a recent study focused on 26 patients with SSc in the Netherlands and France treated with a uniform protocol based on high-dose cyclophosphamide and CD34 selection of autologous grafts with similar eligibility criteria, outcome measures and transplant regimen. With a median follow-up of 5.3 years (range 1–7.5), the Kaplan–Meier estimated survival at 7 years was 84.8% (95% CI 70.2% to 100%) and event-free survival, defined as survival without mortality, relapse or progression of SSc resulting in major organ dysfunction, was 57.1% (95% CI 39.3% to 83%). Two patients died from disease relapse, one from malignancy. Several infectious complications occurred, including three cases of reactivation of herpes zoster and two with atypical mycobacteria, but all resolved with treatment. In line with earlier observations, a more than 50% reduction in skin thickening was observed from baseline in the group as a whole (p<0.001), while pulmonary, renal and cardiac function remained stable in most patients. The most striking finding was the improvement of performance status (0 normal, 4 bedridden) from 2.21 at baseline to 0.6 at 5 years (p<0.05).

Similar data were obtained in the long-term follow-up study of 27 patients with SSc in North America using a transplant regimen which included total body irradiation (800 cGy) with lung shielding, cyclophosphamide (120 mg/kg) and equine antithymocyte globulin (90 mg/kg), followed by CD34-selected haematopoietic cell transplantation. Seventeen of 27 (63%) evaluable patients who survived at least 1 year after HDIT had sustained responses at a median follow-up of 4 years (range 1–8). Skin thickening as assessed by the modified Rodnan skin score and functional ability as determined by the modified Health Assessment Questionnaire Disability Index improved significantly at final evaluation. Skin biopsies confirmed a
significant decrease of dermal fibrosis compared with baseline ($p<0.001$). Lung, heart and kidney function remained clinically stable. There were 12 deaths during the study (eight transplantation-related; four SSc-related). The estimated progression-free survival was 64% at 5 years. The observed sustained responses exceeded those previously reported with other treatments.

Based on these encouraging results prospective, multicentre trials have been launched in Europe and the United States to investigate further the therapeutic value of HDIT + SCT in SSc and other autoimmune diseases. The first of these, the ASTIS trial (Autologous Stem cell Transplantation International Scleroderma trial), started in 2001 under the auspices of the EBMT/EULAR to compare the safety and efficacy of HSCT with that of conventional pulse therapy cyclophosphamide in patients with severe SSc at risk of early mortality. Box 1 lists the study end points of the ASTIS trial. Eligibility criteria include a diagnosis of diffuse systemic sclerosis of recent onset and major organ (heart, kidney, lungs) involvement according to predefined criteria (box 2). Of note, patients who have been extensively pretreated with cyclophosphamide are excluded, as are patients with severe pulmonary hypertension who are at risk of fluid overload (box 3). Figure 1 shows details of both treatments.

At the time of writing this article (July 2008), 123 patients from 25 centres in 10 countries had been randomised to either HSCT ($n=66$) or to the control arm ($n=57$) with a median follow-up of 50 months. The majority of patients were enrolled because of new or progressive lung disease. Interim safety analyses are done regularly, which have led to adjustments of the protocol (eg, administration of antithymocyte globulin). The North American counterpart of the ASTIS trial, sponsored

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**Box 3 ASTIS trial: exclusion criteria**

- Pregnancy or unwillingness to use adequate contraception during study;
- Concomitant severe disease:
  - Respiratory—that is, mean pulmonary arterial pressure $>$50 mm Hg (by cardiac echo or right heart catheterisation), carbon monoxide transfer factor $<$40% predicted, respiratory failure as defined by the primary end point;
  - Renal—that is, creatinine clearance $<$40 ml/min (measured or estimated);
  - Cardiac—that is, clinical evidence of refractory congestive heart failure; left ventricular ejection fraction $<$45% by multigated radionuclide angiography or cardiac echo; chronic atrial fibrillation; oral anticoagulation; uncontrolled ventricular arrhythmia; pericardial effusion with haemodynamic consequences as evaluated by an experienced echocardiograph;
  - Liver failure as defined by a sustained threefold increase in serum transaminase or bilirubin;
  - Psychiatric disorders including active drug or alcohol abuse;
  - Concurrent neoplasms or myelodysplasia;
  - Bone marrow insufficiency defined as leucocytopenia $<$4.0 $\times$ 10$^9$/l, thrombocytopenia $<$50 $\times$ 10$^9$/l, anaemia $<$80 g/l, CD4+ T lymphopenia $<$200 $\times$ 10$^6$/l;
  - Uncontrolled hypertension;
  - Uncontrolled acute or chronic infection, including HIV, human T-lymphotropic virus-1, 2 positivity;
- Previous treatments with total lymphoid irradiation, total body irradiation or alkylating agents including cyclophosphamide ($>$5 g IV cumulative, or $>$3 months oral up to 2 mg/kg body weight);
- Significant exposure to bleomycin, tainted rapeseed oil, vinyl chloride; trichloroethylene or silica; eosinophilic myalgia syndrome; eosinophilic fasciitis;
- Poor compliance of the patient as assessed by the referring doctors.

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**Figure 1** Treatment arms of the ASTIS trial. ATG, antithymocyte globulin; G-CSF, granulocyte-colony stimulating factor.

**Figure 2** Normalisation of nailfold capillaroscopy pattern in a patient with systemic sclerosis treated with high-dose immunosuppressive therapy and autologous stem cell transplantation.
by the National Institutes of Health—the “Scleroderma: Cyclophosphamide Or Transplantation (SCOT) trial”—compares safety and efficacy of a different transplant regimen with intravenous pulse therapy cyclophosphamide. The protocols of the ASTIS and SCOT trials are matched with respect to entry criteria, study parameters, end points and the control arm to facilitate future analyses. Long-term follow-up of patients from these trials is crucial in order to monitor potentially late sequelae or discover delayed diverging trends in (event-free) survival.

The observations of profound clinical effects of HDIT + SCT in autoimmune disease, including SSc, are in essence largely empirical. Although comprehensive translational studies are scarce, evidence is emerging that clinical events are paralleled by fundamental alterations of the immune system: induction of regulatory T cells (juvenile idiopathic arthritis), capillary regeneration (SSc) (fig 2), restoration of T-cell repertoire (multiple sclerosis, SLE), elimination of autoantibody-producing cells (RA, SLE) and remodelling of fibrosis (SSc). Nevertheless, the relationship between clinical outcome and immune effects is complex, as shown by the persistence of T-cell receptor abnormalities and autoantibodies in transplanted patients with SSc.

Stem cell transplantation has evolved into an established treatment for patients with severe rheumatic autoimmune disease, including patients with diffuse SSc at risk of premature mortality. Treatment-related toxicity is significant, however, and whether the benefits of this new treatment modality outweigh the risks can only be determined through prospective randomised trials, such as the ASTIS and SCOT trials.

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Competing interests: None.

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