# Emerging use of Stem Cell Transplants for Systemic Sclerosis

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**Abstract**

Over the last 20 years, stem cell transplant (SCT) has shown promising results in a variety of autoimmune rheumatologic disorders. Of these conditions, systemic sclerosis (SSc) has garnered the most attention given the limited alternative options for advanced disease. Several early studies and now several randomized controlled trials have demonstrated improved skin, lung, and vascular outcomes. However, complications associated with the immunoablating steps in the transplant process have led to cardiotoxicity, infections, and death in some transplant recipients. Growing efforts are being made to examine how to optimize the transplant process to improve safety but retain efficacy.

**Keywords:** stem cell transplant; systemic sclerosis.

## 1. Introduction

The advancement of stem cell transplant (SCT) for autoimmune rheumatologic diseases has continued to be an area of investigation. Among the rheumatologic disorders, systemic sclerosis (SSc) remains the most widely studied. This continued pursuit of SCT in SSc is driven largely due to the limited effective treatment options available for this condition.

SSc is a fibrosing multisystem disorder that can affect the skin, lungs, gastrointestinal tract and pulmonary vasculature [1-3]. There are 2 major categories, limited and diffuse, distinguished by the extent of skin involvement. Diffuse SSc is associated with higher incidence of heart, lung, and kidney involvement and carries a 5-10% per year mortality risk [4,5]. For patients with such severe, refractory autoimmune conditions SCT has emerged as a treatment with great promise.

SCT essentially works by expunging the disease causing pro-inflammatory immune system and later repopulating it with harvested stem cells; it has been likened to a resetting of the immune system [6,7]. There are several steps in the transplant process. Cells must first be mobilized often with cyclophosphamide and growth-colony stimulating factor (G-CSF). The mobilized cells are harvested and the recipient then generally undergoes an immunoablative conditioning regimen, often including cyclophosphamide and anti-thymocyte globulin (ATG), before the cells are infused.

The majority of SCTs in scleroderma utilize hematopoietic stem cells, which are capable of differentiating into cells belonging to both myeloid and lymphoid lineages [8]. Hematopoietic stem cell transplants (HSCTs) are mobilized from either the patient (autologous) or from another individual, typically an HLA-identical sibling or unrelated donor (allogenic). Prior to transplantation, the harvested cells often may be manipulated to deplete or select for certain cell types. CD34+ selection is often employed to select for hematopoietic stem cells, thus eliminating T cells [9].

 

**2. Use of Hematopoietic stem cell transplant in Systemic Sclerosis**

The European Group for Blood and Marrow Transplantation (EBMT) Autoimmune Disease Working Party (ADWP) has maintained a database on patients receiving HSCT in Europe. As of 2015, 433 patients with SSc have been registered [10]. Early data yielded positive results with patients achieving reductions in disease severity. In 2007, a pilot phase II single-arm study with high dose immunosuppressive therapy and HSCT was performed in 34 patients with poor prognosis SSc. Patients demonstrated a significant decrease in modified Rodnan skin scores (mRSS) but there was a high rate of treatment related mortality (TRM) at 23% [11]. Also in that year, a phase I study with 10 SSc patients reported improved mRSS and 90% survival and 70% progression free survival at a mean 25.5 months follow-up [12]. Later in 2012 a cohort study of 26 SSc patients demonstrated significant improvements in mRSS and mean inspiratory vital capacity [13]. These studies helped set the framework for several randomized clinical trials (RTCs) that have been done or are currently ongoing in the field of HSCT and SSc. Table 1 illustrates these studies and their transplant regimens.

The phase II American Scleroderma Stem Cell versus Immune Suppression Trial (ASSIST) was the first of the 3 studies; it was published in 2011. This was a small sized study restricted to patients younger than 60 years of age with either interstitial lung disease or those with other organ involvement who had mRSS>14. 10 patients were randomized to autologous HSCT with cyclophosphamide and ATG and 9 were randomized to monthly intravenous cyclophosphamide. At 12 months, none of the monthly cyclophosphamide patients improved, however all of the HSCT patients improved achieving primary endpoints defined as an improvement of >25 % in the mRSS or >10 % improvement in their forced vital capacity. There was no treatment related mortality (TRM) reported. [14•].

The larger phase III Autologous Stem Cell Transplantation International Scleroderma (ASTIS) trial was published in 2015. It included patients from the EBMT; it was a 2 year multi-centre RCT. 79 patients were randomized to

 

autologous HSCT following high dose cyclophosphamide and ATG for conditioning with CD34+ HSC selection and 77 were randomized to receive high dose monthly intravenous cyclophosphamide. The HSCT arm had a significantly prolonged event-free survival and overall survival over a median 5.8 year follow-up. Secondary endpoints demonstrated improvement in the HSCT group with regard to quality of life, mRSS, pulmonary function, particularly forced vital capacity and total lung capacity [15••].

Unlike ASSIST, this larger study did report several TRMs including 19 deaths and 3 irreversible organ failures in the HSCT group as well as 23 deaths and 8 irreversible organ failures in the cyclophosphamide group. Of note, TRM was highest in the early stages of follow-up in the autologous HSCT group. However long-term event-free and overall survival rates were higher in the autologous HSCT than in the control group [15••]

The third RCT is a large ongoing prospective clinical trial in North America evaluating HSCT in SSc, the Scleroderma Cyclophosphamide or Transplant (SCOT) trial. The SCOT trial is a phase II/III randomized study comparing myeloablative (total body irradiation and cyclophosphamide) autologous HSCT versus monthly cyclophosphamide with similar endpoints as the ASTIS trial [16]. The recruitment phase for the SCOT trial is now complete, however results have not yet been released [17].

### 3. Use of Stem Cell Transplant for localized manifestations of Scleroderma

In the last several years innovative use SCT for non-life threatening SSc has emerged with particular applications for cutaneous and peripheral vascular phenomena. Several of these small studies have looked at the use of multipotent adipose derived stem cells (ADSC), which possess increased expression of vascular endothelial growth factor, basic fibroblast growth factor and interleukin-6 and can also secrete anti-inflammatory soluble factors including interleukin-10, interferon-γ, and transforming growth factor-β [18, 19].

For these non-life threatening manifestations, the stem cells have been transplanted directly into subcutaneous or ischemic tissues. This local transplant

 

technique does not necessitate the mobilization or immunoablative steps associated with more standard HSCT regimens. Table 2 highlights some of the recent studies evaluating SCT on local scleroderma. These have yielded improved skin thickening, digital ulcers, and pain [20-23]. Additional larger studies would be needed to draw more firm conclusions on the benefits of localized delivery of stem cells.

**4. Cardiopulmonary Risks related to Transplant Related Mortality**

One of the critical questions to arise from the past 20 years of SCT in SSc is how to identify risk factors related to TRM. TRM is defined by the Milan consensus as death within the first 3 months of transplant [24]. Early cases of HSCT in SSc revealed higher cardiac related mortality which has spawned early recommendations on cardiac pre-screening prior to SCT [25]. In 2012 the EMBT released updated guidelines on SCT for autoimmune diseases; several pre-screening HSCT criteria were outlined to better focus patient selection. Table 3 summarizes these organ specific guidelines. For SSc patients advanced cardiac disease defined as a left ventricular ejection fraction < 50%, uncontrolled ventricular arrhythmias, pericardial effusions > 1 cm, were exclusion cardiac criteria. Respiratory disease including diffusing capacity of the lung for carbon monoxide (DLCO) <40% predicted, mean pulmonary artery pressure >50mmHg, and renal insufficiency defined as a creatinine clearance <40ml/min per $m^2$, were also criteria for exclusion. Pre-screening testing for infections was also addressed in the guidelines. It included Herpes simplex virus (HSV), Varicella zoster virus (VZV), Epstein - Barr virus (EBV), human immunodeficiency virus (HIV), human T-lymphotropic virus type 1 and 2, hepatitis viruses and toxoplasmosis, and any other infection screening appropriate for the geographical location. [26••].

Outside of the EBMT cardiac guidelines, other recommendations have been proposed including pre-screening echocardiography with tissue Doppler and quantitative assessment of right ventricular function (e.g. tricuspid annular plane systolic excursion) right heart catheterization with fluid challenge, cardiac magnetic resonance imaging with

 

gadolinium contrast (including T1 mapping for assessment of diffuse myocardial fibrosis) [27-29].

Recent data support the pulmonary criteria by the EMBT. In a retrospective study over a 5 year period, N Del Papa et al. asserted that lower TRM may have potentially been attributed to excluding patients with a DLCO below 50% of predicted value in the retrospective study of 18 patients with SSc [30]. Smoking history is another proposed exclusion criteria. In *post hoc* analysis of the ASTIS trial 7 of the 8 cases of TRM in HSCT arm involved patients who had a smoking history [15, 31].

## 5. Transplant Protocol Risks related to Transplant Related Mortality

In addition to evaluating risks associated with patient selection, another area of investigation that can affect TRM involves the specific transplant protocols. There are potential variances at every step of the transplant process, each of which may have differing impacts on TRM or serious adverse effects. The first area to consider is the donor source of the cell. Typically transplants are done with autologous cells; allogenic cells have fallen out of favour given the risks of graft versus host disease [31]. However, emerging use of other cell sources including adipose derived cells for non-life threatening scleroderma would also likely have an impact on risk of TRM.

Mobilization is another step in the transplant process that can vary. Blank N, et al performed a retrospective comparison of chemotherapy with cyclophosphamide 2 doses of 2 g/m$^2$ and 1 dose of 2 g/m$^2$ and found comparable mobilization results in patients with several autoimmune diseases including 15 patients with SSc [32]. This study provides a rationale for potentially lowering cumulative cyclophosphamide dosing.

After cells are mobilized, some protocols call for CD 34+ selection, a process that may delay immune reconstitution and lymphocyte ontogeny [33,34]. Cell selection also increases the cost of transplant, reduces the number of stem cells available for infusion, and predisposes the material to potential contamination by handling [35,36]. In 2016, a review of 138 SSc patients found that CD34+ selection did not yield any statistical significance on overall survival.

 

Additionally there were no significant differences for progression of SSc or incidence of relapse [37]. In the 2012 EBMT guidelines no significant evidence was felt to support *ex-vivo* graft manipulation [26••].

Conditioning regimens are an emerging area of investigation as well. In a smaller study of 6 patients, lower dose cyclophosphamide 1 g/m$^2$ along with thiotepa, an alkylating agent with no known cardiotoxicity, demonstrated effectiveness in SSc patients with cardiac involvement [38]. A larger RCT is also recruiting patients. As a follow-up to the initial ASSIST trial, ASSIST II plan to compare the ASSIST I conditioning regimen of cyclophosphamide and rabbit ATG to a less intense regimen of rabbit ATG/cyclophosphamide/Fludarabine. The cyclophosphamide dose will be decreased to 120mg/kg (60mg/kg/day x 2) compared to 200mg/kg (50mg/kg/day) in the standard regimen used in ASSIST I in efforts to lower cardiotoxic risks [39].

### 6. Patient Selection

SCT should be considered a treatment option for select SSc patients. The 2012 EBMT guidelines recommended autologous HSCT be considered in diffuse SSc patients with disease duration ≤ 5 years since development of first non-Raynaud's symptoms, have a mRSS ≥15, and have major organ involvement (pulmonary, cardiac, or renal) with evidence of onset or clinically significant worsening in the previous 6 months. Pulmonary criteria were defined as a DLCO ≤70% of predicted plus evidence of interstitial lung disease on a chest radiograph or high resolution computerized tomography scan. Cardiac involvement included second and third-degree atrioventricular block, intra-ventricular conduction disturbance, left axis deviation, atrial or ventricular rhythm disturbance, and pericarditis as defined by ≤1 cm on cardiac ultrasound. Finally, renal was proteinuria >0.3 g/24 h, without other explanation other than SSc [26••]. Table 4 highlights these characteristics of patients that may be potential candidates for HSCT. Patients deemed appropriate candidates for SCT should be considered for referral to medical centres with expertise and experience in SCT.

 

## 7. Conclusion

SCT in SSc is providing new areas of promise for a condition with otherwise limited treatment options. Large RCTs have now demonstrated significant improvements in organ involvement and survival. Despite positive results, TRM remains a major concern. Prescreening of patients undergoing SCT can lower this risk. Future studies evaluating optimal transplant protocols that will preserve efficacy but lower risks are ongoing. Final results from the SCOT and ASSIST II trials are expected to provide important insights moving forward.

## Disclosure

No potential conflicts of interest relevant to this article were reported.

 

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**Table 1.** Randomized Controlled Trials of Hematopoietic Stem Cell Transplant in Systemic Sclerosis

| | ASSIST I [14•] | ASTIS [15••] | SCOT [16,40] | ASSIST II [39] |
|---|---|---|---|---|
| Control regimen | Monthly IV CYC 1 g/$m^2$ x 6 doses doses | Monthly IV CYC 750 mg/$m^2$ x 12 doses | Monthly IV CYC 750 mg/$m^2$ x 12 doses | Monthly IV CYC 1 g/$m^2$ x 6 doses |
| Test Regimen | | | | |
| Mobilization | CYC 2 g/$m^2$ +G-CSF 10µg/kg | CYC 4 g/$m^2$ + G-CSF | CYC 4 g/$m^2$ +G-CSF | CYC 2 g/$m^2$ + G-CSF 10µg/kg |
| Conditioning | CYC 200 mg/kg + Rabbit ATG 0.5-1.5 mg/kg with IV MP 1,000mg | CYC 200 mg/kg + rabbit ATG 75 mg/kg | 800cGY TBI (in two 200cGY fractions BID) +CYC 120 mg/kg + equine ATG | CYC 120 mg/kg + rabbit ATG + Fludarabine |
| Graft manipulation | none | CD34+ selection | CD34+ selection | none |

*IV CYC*=intravenous cyclophosphamide, *G-CSF*=Growth-colony stimulating factor, *ATG*=anti-thymocyte globulin, *MP*=methylprednisolone

 

**Table 2.** Recent Studies Regarding Local Applications of Stem Cells for Localized Scleroderma Features

| Study [Reference] | Patients | SCT | Inclusion features | Results |
|---|---|---|---|---|
| Del Papa N, et al. [20] | 15 | autoADSC | SSc related digital ulcers | Improved digital ulcers, pain |
| Scuderi N, et al. [21] | 6 | autoADSC | localized scleroderma (linear and plaque scleroderma, Generalized morphea) | Improved skin exams, regression of dyschromia, arrest of local disease progression |
| Granel B, et al. [22] | 12 | autoSVF | SSc with CHFS score >20/90 | Improved CHFS score, mRSS, RCS |
| Takagi G, et al. [23] | 40 | autoBMMC | SSc with digital ulcer or gangrene | Decreased pain, improved $TcPO_2$ |

*Auto*= autologous, *ADSC*=adipose derived stem cells, *SSc*=systemic sclerosis, *SVF*= adipose-derived stromal vascular fraction, *CHFS*=Cochin hand function scale, *mRSS*= modified Rodnan skin score, *RCS*=Raynaud condition score, *BMMC*=bone marrow mononuclear cells, $TcPO_{2=}$ transcutaneous oxygen tension

 

**Table 3.** Organ Specific Exclusion Criteria for HSCT in Systemic Sclerosis Patients according to the 2012 European Group for Blood and Marrow Transplantation Guidelines [26••]

| Exclusion Criteria | |
|---|---|
| Cardiac | Left ventricular ejection fraction < 50% |
| | Uncontrolled ventricular arrhythmias |
| | Pericardial effusions > 1 cm |
| Pulmonary | Diffusing capacity of the lung for carbon monoxide (DLCO) <40% predicted, |
| | Mean pulmonary artery pressure >50mmHg |
| Renal | Creatinine clearance <40ml/min per $m^2$ |

 

**Table 4.** Characteristics of Potential Candidates for HSCT according to the 2012 European Group for Blood and Marrow Transplantation Guidelines [26••]

- Diffuse SSc
- Disease Duration ≤ 5 years since development of first non-Raynaud's symptoms
- mRSS ≥15
- Any of the following major organ involvement
    - Pulmonary
        - DLCO ≤70% of predicted
          *and*
        - ILD on a imaging
    - Cardiac
        - Second and third-degree atrioventricular block
        - Intra-ventricular conduction disturbance
        - Left axis deviation
        - Atrial or ventricular rhythm disturbance
        - Pericarditis ≤1 cm on cardiac ultrasound
    - Renal
        - Proteinuria >0.3 g/24 h
- Disease onset or clinically significant worsening in previous 6 months

SSc= systemic sclerosis, mRSS= modified Rodnan Skin Score, *DLCO* = diffusing capacity of the lung for carbon monoxide, *ILD*= interstitial lung disease.

 