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Everything you always wanted to know about systemic sclerosis but were afraid to ask: Part 6. Autologous stem cell transplantation as a therapeutic option in scleroderma

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Everything you always wanted to know about systemic sclerosis but were afraid to ask: Part 6

Autologous stem cell transplantation as a therapeutic option in scleroderma

Short title: Transplantation in scleroderma

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Abstract

Scleroderma is an immune disease characterized by vascular abnormalities, inflammatory and progressive fibrosis of skin and internal organs. The worst prognosis, with high risk of early mortality, is in the case of visceral organ involvement (lung, digestive system and heart). The treatment is based on steroids, immunosuppressive medications but the prognosis is still very poor. Autologous stem cell transplantation (autoHSCT) still remains the promising option which can achieve long remission. In many years since the first autoHSCT in scleroderma almost 1000 patients have undergone the procedure. AutoHSCT is recommended with a grade I level of evidence for therapy of severe rapidly progressive scleroderma by the European Society for Blood and Marrow Transplantation (EBMT) Autoimmune Diseases Working Party (ADWP) guidelines.

Key words: autologous stem cell transplantation; autoHSCT; scleroderma; autoimmune disease

Introduction

Autologous stem cell transplantation (autoHSCT) is one of the methods which for many years has been known as an effective therapy in hematological disorders [1]. The idea of using high dose chemotherapy with autologous stem cell transplantation occurred in 60s of XX century [2]. Transplantation is the supporting therapy for reducing the myelotoxicity of conditioning

regimen (treatment immediately before autoHSCT). Therefore, this procedure allows for safe use of high dose therapy in hematological but also others, non-hematological disorders.

Scleroderma is an immune disease characterized by vascular abnormalities, inflammatory and progressive fibrosis of skin and internal organs [3]. The manifestation is heterogeneous. Skin changes such as thickness are the most typical. The worst prognosis is in the case of visceral organ involvement (lung, digestive system and heart). These patients are at high risk of early mortality. The treatment is based on steroids, immunosuppressive medications (e.g., cyclophosphamide, methotrexate), but the prognosis is still very poor [4]. AutoHSCT continually remains the promising option which can provide long remission. In almost 25 years since the first autoHSCT in scleroderma, more than 800 patients have undergone the procedure. It is the second most common autoimmune disorder to be treated with autoHSCT, after multiple sclerosis. AutoHSCT is recommended with a grade I level of evidence for therapy of severe rapidly progressive scleroderma by the European Society for Blood and Marrow Transplantation (EBMT) Autoimmune Diseases Working Party (ADWP) guidelines [5].

Indication in immune disease

In scleroderma, indication for autoHSCT is severe rapid progression and early but not end-stage visceral organ involvement (Figure 1). AutoHSCT should be performed in experience centers with Joint Accreditation Committee ISCT-Europe (JACIE) and EBMT accreditation, where experts from hematopoietic stem cell transplant cooperate with rheumatologists [6]. Figure 1 shows the indications for autoHSCT.

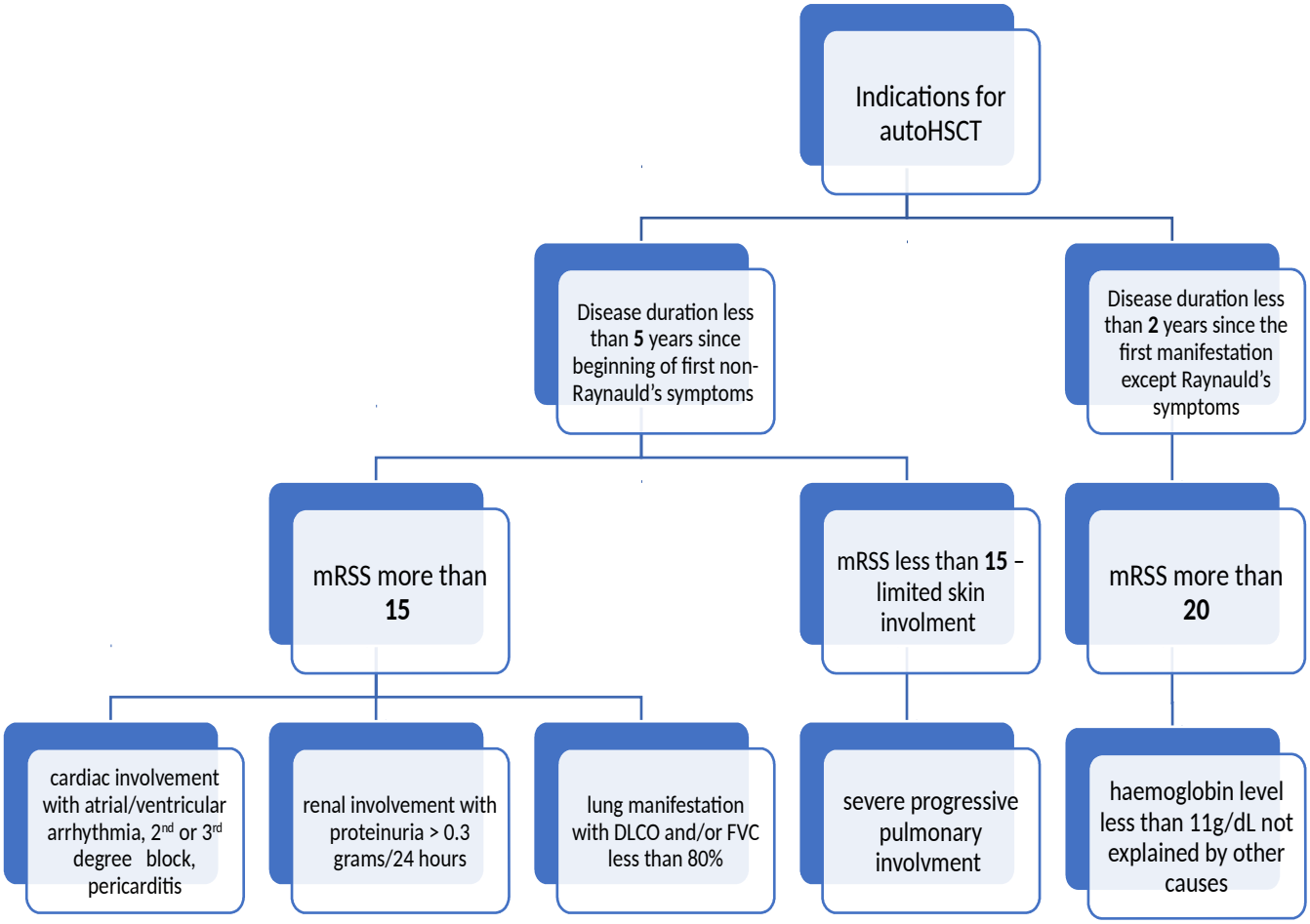

Figure 1. Indications for autologous stem cell transplantation in systemic scleroderma. DLCO — diffusing capacity of carbon-monoxide; FVC — forced-vital-capacity; mRss — modified Rodnan skin score

Patients diagnosed within 5 years with moderate lung involvement and rapid skin progression are considered as most likely to benefit from autoHSCT.

Contraindications for autoHSCT: age higher than 65, active smoking, pregnancy, neoplasm, major organ involvement (Tab. 1) [6].

Table 1. Organ damage

Organ	**Involvement**
Lung	Arterial oxygen pressure at rest less than 60 mm Hg Arterial pressure in carbon dioxide at rest more than 50 mm Hg Pulmonary arterial hypertension
Heart	Refractory congestive heart failure

	Left ventricular ejection fraction less than 45% Severe coronary artery disease Pulmonary artery resistances Uncontrolled ventricular arrhythmia Heart tamponade
Kidney	Renal failure (GFR < 40 mL/min)
Liver	Twice normal transaminases and/or bilirubin Albuminemia < 20 mg/L

GFR — glomerular filtration rate; mm Hg — millimeters of mercury; mg — milligram; min — minute; ml — milliliter; L — litter

Mechanism of the method

AutoHSCT is a procedure using the possibility of intensive immunoablative therapy, which is supported by hematopoietic stem cell transplantation. The primary purpose of the procedure is to reset the immune system by means of chemotherapy and to replace the defective system with a new one, formed from the transplanted cells [7]. After autoHSCT, reconstitution first occurs in B lymphocytes, NK cells and CD8+ T lymphocytes [8]. Depletion of CD4+ T lymphocytes may persist even for a few years. CD4+ cells are known to secrete profibrotic as well as proinflammatory cytokines which can directly contribute to local tissue fibrotic processes. It is a key in the pathogenesis in scleroderma but also could be the effective therapeutic mechanism in autoHSCT [9].

The procedure consists of two parts (Fig. 2).

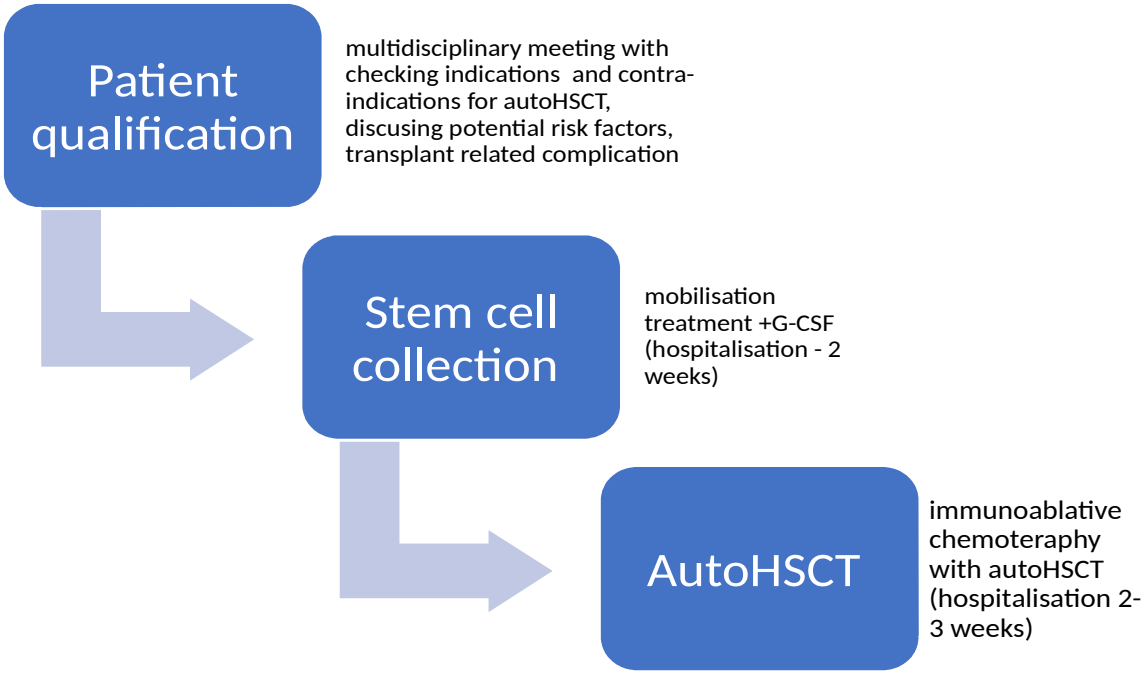

Figure 2. The steps of the procedure of autologous stem cell transplantation (autoHSCT). GCSF — granulocyte colony stimulating factor

The first one is collection of hematopoietic stem cells from peripheral blood.

All patients received stem cell mobilization treatment which helps cells to be mobilized to peripheral blood. Typically, it is cyclophosphamide in a total dose of 4 g/m^2 intravenously (*i.v.*) and granulocyte colony stimulating factor (G-CSF) 10 ug/kg of body weight from day 5 of mobilization treatment to the day of peripheral blood stem collection [8]. Leukapheresis — stem cell collection is started when the number of hematopoietic stem cells is more than 0.025 x 10^9/L in peripheral blood (Fig. 3). Cell enumeration is performed using the fluorochrome-conjugated monoclonal antibodies — anti-CD34. The minimal number of CD34+ cells for safety autoHSCT is 2–3 x 10^6/kg body weight (b.w.). After collection, the hematopoietic cells are frozen using cryopreservation.

The second part is started after several weeks to a month. Before autologous transplantation conditioning treatment is given. The whole mechanism is using the high dose chemotherapy +/– antithymocyte globulin (ATG) or, less often, total body irradiation (TBI) followed by re-infusion of CD34+ cells to patient's peripheral blood (Fig. 4) [8]. Reconstitution of the blood cells in the bone marrow takes about two weeks.

Figure 3. Hematopoietic stem cell collection from peripheral blood

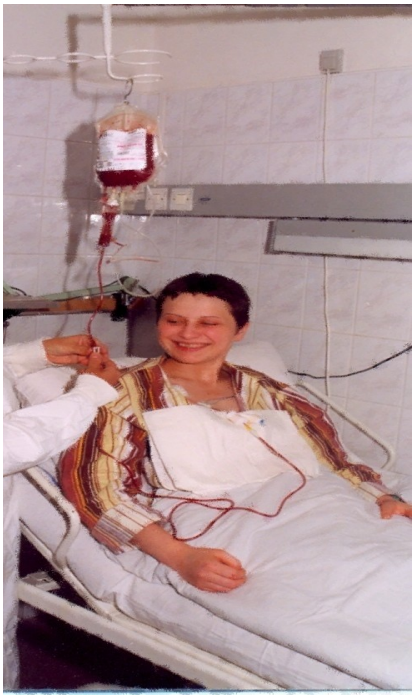

Figure 4. Hematopoietic stem cell transplantation

The results

The goal of autoHSCT in scleroderma is to improve function of the involved organs, and this method can provide superior long-term outcomes. The rapid regression was observed in skin fibrosis, which was confirmed by skin histology biopsy [10]. The most important regression

was observed in lung fibrosis, which had never been observed with any other therapy. Time of the post-transplant remission is even up to 20 years, but ordinarily between 5–7 years [11].

Side effects

Transplant-related toxicity and infections remain the main complication after autoHSCT in scleroderma [6].

Cardiotoxicity remains to be the main limitation of this method of treatment. Cardiac involvement in scleroderma may determine whether transplantation is successful [12]. One should remember that additional fever, infections in the course of post-therapeutic neutropenia and parenteral hydration necessary both during mobilization and conditioning treatment may increase the risk of cardiac complications. Before qualification for autoHSCT, it is necessary to perform assessment of cardiac capacity, based not only on an electrocardiographic or ultrasound scan examination, but also on magnetic resonance imaging of the heart, which increases chances of detecting hidden abnormalities.

Infections are another early complication which may have a significant impact on patient survival. It is also one of the most common causes of death [6, 11] Development of pulmonary infection, especially soon after transplantation, may pose a fatal threat, especially to patients with respiratory system dysfunction. Adequate prophylactic protection with anti-infective agents during the procedure, and exclusion of potential infection foci, especially dental and laryngological ones, may significantly limit the rate of this complication.

A late complication of autoHSCT may be, for example, fertility disorders. Therefore, before the commencement of the procedure, patients of childbearing age are informed about this complication. Protection of reproductive cells before autoHSCT is one possible option of avoiding it. On the other hand, using cyclophosphamide-based conditional treatment is associated with better fertility than TBI regimen. The EBMT reports showed that pregnancies after autoHSCT for patients with scleroderma are possible [6].

The most dangerous late complication of autoHSCT is an increased risk of neoplasms. The use of high-dose chemotherapy causes rest of the immune system, which, on one hand, is an important basis of treatment, but on the other hand reduces immune alertness, thereby increasing the risk of developing neoplastic diseases. Fortunately, this complication is extremely rare [13].

Randomized trials

The first randomized clinical trial (ASSIST) was performed between 2006–2009 by Burt et al. and included 19 patients (Tab. 2). Ten patients in autoHSCT group had minimal response. Improvement at a year after treatment was defined as a decrease in modified Rodnan skin score (mRss) or an increase in forced vital capacity (FVC). Transplant-related mortality (TMR) was 0. Two patients developed disease progression [14].

The second randomized study was the European Autologous Stem Cell Transplantation International Scleroderma (ASTIS) trial. The number of patients in both arms was as follows: autoHSCT — 71, cyclophosphamide therapy — 57. In this study, CD34+ selected stem cells were used. In the results, event-free survival (EFS) was statistically higher in autoHSCT group than in the control group. The side effects and mortality also were higher in this group but only in the first year of treatment. At 4-year follow-up the number of deaths was higher in the control group [15].

The last controlled study was the Scleroderma Cyclophosphamide or Transplantation (SCOT) trial. In this multicenter, randomized trial, 75 patients with severe scleroderma and visceral organ involvement were included. In contrast to previous studies, lower dose of cyclophosphamide was used, not rabbit but horse ATG and TBI as conditioning regimen were applied (Tab. 2). The results proved that autoHSCT arm was associated with better outcomes (only 9% of transplant recipients had scleroderma relapse) but with more serious adverse events in the early stage of the study. However, 11-year survival was 80% in autoHSCT arm versus 52% in the control group [16].

Table 2. Comparison of clinical trials of autologous stem cell transplantation (autoHSCT) in scleroderma

	ASSIST	**ASTIS**	**SCOT**
Stem cell mobilization	CYC 2 g/m^2 and G-CSF	CYC 4 g/m^2 and G-CSF	G-CSF without CYC
CYC arm	CYC 1000 mg/m^2/month IV × 6 (total 6 g/m^2 over 6 months)	CYC 750 mg/m^2/month IV × 12 (9 g/m^2 over 12 months)	CYC 750 mg/m^2/month IV × 12 (9 g/m^2 over 12 months)

	ASSIST	**ASTIS**	**SCOT**
autoHSCT arm	CYC 200 mg/kg and ATG (rabbit) 6.5 mg/kg	CYC 200 mg/kg and ATG (rabbit) 7.5 mg/kg	CYC 120 mg/kg, ATG (horse) 90 mg/kg, TBI 800 cGy (lung and kidney 200 cGy)
Hematopoietic cells	Unselected	CD34 + selected	CD34+ selected

ASTIS — autologous stem cell transplantation international scleroderma; SCOT — scleroderma cyclophosphamide or transplantation; ATG — anti-thymocyte globulin, CYC — cyclophosphamide; G-CSF — granulocyte colony stimulating factor; HSCT — hematopoietic stem cell transplant; TBI — total body irradiation

Our experiences

Between 2003 and 2016 18 patients with scleroderma underwent autoHSCT at the Department of Hematology and Bone Marrow Transplantation in Katowice [17]. The main indication for transplant was progressive or poorly responded systematic sclerosis. Median age at autoHSCT was 51 (range 24–68). All patients had suffered from scleroderma for less than 10 years. The inclusion criteria were as follows: mRss was less than 15, pulmonary involvement with FVC between 80–40% or decline in FVC more than 10% or DLCO more than 15% on serial testing. The exclusion criteria were: pulmonary arterial hypertension, renal or cardiac insufficiency, FVC less than 40%. Hematopoietic stem cells were collected from peripheral blood after mobilization treatment (cyclophosphamide 4 g/m^2 *i.v.*) followed by G-CSF (dose 10 ug/kg b.w.) until apheresis. All patients collected a sufficient number of CD34+ cells for autoHSCT. There were no life-threatening complications during mobilization; no blood transfusion was needed. Most of conditioning treatment consisted of cyclophosphamide (200 mg/kg) and antiCD52 (alemtuzumab; median dose 60mg). The recovery was as follows: neutrophil count > 0.5 x 10^9/L was achieved after median of 10 days, platelet count > 20 x 10^9/L — after median of 5 days. Four patients died during an early period after transplant with

the main cause of death — pneumonia, followed by sepsis shock. Eleven patients were alive after median follow-up after autoHSCT of 42 months. In this group of patients, we observed a significant reduction in mRss at one year after the procedure [17].

Conclusion

AutoHSCT could be an effective therapeutic option for patients with severe and progressive systemic scleroderma, especially when conventional therapy fails [5]. Previous studies have shown promising results regarding long-term improvement in skin thickness and respiratory function [11, 18]. However, we should not forget of high treatment-related mortality. According to randomized trial and our experience, the highest mortality is within the first year after autoHSCT [15–16]. Many factors could have influenced the outcome of the procedure: conditioning treatment intensity, disease duration, co-morbidities, especially related with scleroderma (heart insufficiency with decreased LVEF, pulmonary arterial hypertension). One should keep in mind that the experience of the transplant center may play a role in decreasing mortality. The cooperation between transplantologists and rheumatologists is also very important because it helps to better prepare the patient for autoHSCT and detect hidden dysfunction of vital organs.

It should be remembered that the risk of early complications and mortality must be weighed against the potential long-term benefits.

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Conflict of interest

None declared.

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