

## CASO CLÍNICO

# Autologous stem cell transplantation in a patient with severe systemic sclerosis

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## ABSTRACT

Systemic Sclerosis (SSc) is a chronic disease of the connective tissue, whose pathogenesis involves abnormalities of the immunological system. It has a variable course and there is a subgroup of patients with rapidly progressive disease or unresponsive to conventional treatment. These patients can benefit from intensive immunosuppression and autologous hematopoietic stem cell transplant.

**Clinical case:** 19-year-old (y.o.) woman diagnosed with SSc at the age of 13 y.o. with cutaneous, vascular and articular involvement with initial response to methotrexate. Three years later the disease progressed with severe digestive involvement (dysphagia, delayed gastric emptying and weight loss) needing gastrostomy for nutritional support. She was treated with cyclophosphamide without improvement. In May 2012 she had an autologous transplant with myeloablative regimen (BEAM): carmustine 300 mg/m<sup>2</sup> x1day; etoposide 120 mg/kg x4days; cytarabine 120 mg/kg 12/12:h x4days; melphalan 140 mg/m<sup>2</sup> x1day. A year and a half after transplantation she is asymptomatic, without any signs or symptoms of the disease, feeds by mouth and the gastric emptying study is normal. Currently she is free of medication.

**Keywords:** Systemic sclerosis; Autologous Hematopoietic Stem Cell Transplant;

## INTRODUCTION

Systemic sclerosis (SSc) is a progressive disease, whose pathogenesis includes early immunological events and vascular alterations, especially at the beginning of

the disease<sup>1,2</sup>. Until now, there is no proven effective therapy for this disease<sup>3</sup>. A subgroup of patients has a rapidly progressive disease or is refractory to conventional treatment and these patients can benefit from intensive immunosuppression and rescue with Autologous Hematopoietic Stem Cell Transplant (AHSCT). The justification for the AHSCT was validated by studies in animal models of autoimmunity and later in phase I/II/III studies in the framework of the European Bone Marrow Transplantation (EBMT)<sup>6,7</sup>.

## CLINICAL CASE

Young female, 19 y.o., with SSc diffuse subtype, diagnosed at 13 y.o., with cutaneous, vascular and articular involvement. She had severe Raynaud's phenomenon since 11 y.o. and, at diagnosis, presented with digital ulcers, skin thickening (modified Rodnan skin score 17,5) and elbow and knee contractures. Nailfold capillaroscopy showed a scleroderma pattern and she had positive antinuclear antibodies (1:1280, nucleolar staining pattern) and anti-Ro 52. Skin thickness and joint contractures improved with methotrexate but intermittent infusions of iloprost and administration of endothelin receptor antagonist (bosentan) were needed due to the very painful digital ulcers. Three years after diagnosis she started severe complaints of gastrointestinal reflux, dyspepsia and dysphagia. Gastrointestinal endoscopy showed chronic gastritis and esophagitis; esophageal manometry revealed a lower esophageal sphincter pressure and weak pressure waves (1/3 lower esophagus hypo-contractility) in the smooth muscle. Gastric scintigraphy showed 26% emptying at 2 hours. There was no improvement with medication (esomeprazol, domperidona, erythromycin and even cisapride) and there was progression of the disease progressed. Therefore, cyclophosphamide (Cy) and intravenous IV immunoglobulin had been tried for 3 months. There was an initial mild relieving of the

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symptoms and of the gastric emptying in the scintigraphy (53% at two hours), but dysphagia and dyspepsia remained a major concern. The symptoms progressed and she became intolerant to solid foods, with subsequent relevant weight loss and needed gastrostomy for nutritional support.

Due to the severity of the disease without response to conventional therapy and the poor quality of life she was proposed for AHSCT. On January of 2012 she was treated with intermediate dose of immunosuppressive therapy (cyclophosphamide (Cy) 4 gr with uromitexan (Mesna) and cautious hyperhydration) followed by hematopoietic growth factors (G-CSF) for mobilization and collection of peripheral stem cells progenitors. [Table I].

On May 2012 she had an AHSCT with myeloablative BEAM regimen (carmustine 300 mg/m<sup>2</sup> x1day; etoposide 120 mg/kg x4days; cytarabine 120 mg/kg 12/12:h x4days; melphalan 140 mg/m<sup>2</sup> x1day)<sup>4,5</sup> [Table – II] and infusion of unmanipulated blood stem cells (CD34 + = 2.7 x10<sup>6</sup>/kg). She had expected complications after bone marrow transplantation: a grade 3 mucositis with the need of opioid analgesia and total parenteral nutrition for 5 days; a cutaneous herpes zoster and a febrile syndrome without clinical focus of infection and no isolated agent. Hematopoietic recovery was as on day +10 for PMN > 500/mm<sup>3</sup> and at day + 11 for platelets > 20000/mm<sup>3</sup>. Hospital discharge day was at day +17 *post* transplant. Immediately after discharge, the patient had good oral food tolerance (without the need for nutritional supplementation by gastrostomy) and cutaneous and vascular improvement.

A year and a half after autologous transplantation the patient is completely asymptomatic, without any clinical evidence of the disease. She had never had Raynaud's and the gastric emptying and motility are normal and she has already withdrawn the gastrostomy. Currently the patient is free of medication.

**TABLE I. MOBILIZATION PHSC REGIMEN**

	R					
Cy	x	x				
G-CSF			x	x	x	Peripheral CD34+ cells>10x10 <sup>6</sup> /kg
						PHSC

Cy: Cyclophosphamide 2 g x 2d + G-CSF: Hematopoietic growth factors 10mcg/Kg/d; R: recovery; PHSC: peripheral hematopoietic stem cell

## DISCUSSION

This case reports the first AHSCT performed for an autoimmune disease in Portugal. We would like to emphasize the sequential therapy approach with cyclophosphamide in intermediate dose followed by myeloablative/immunoablative BEAM therapy and autologous hematopoietic rescue, considering their possible synergistic effect. The choice of mobilization regimen was Chemotherapy (Cy) with G-CSF because priming chemotherapy is recommended to enhance mobilization while maintaining disease control and preventing potential flare, which could be a consequence of G-CSF alone<sup>6</sup>. The subsequent condition regimen (BEAM) seemed the best option in this patient, not only because she didn't have evidence of pulmonary damage (and therefore we prevented BCNU toxicity) but also because it is known that the conditioning regimen be of "intermediate intensity" is associated with a low transplant rate mortality. Other options such as "high intensity" conditioning regimens (including total body irradiation TBI or high-dose regimens containing busulphan) or even "low-intensity" conditioning (referring to cyclophosphamide alone, melphalan alone and fludarabine-based regimens) were associated with poor improved outcomes when compared with to "intermediate intensity" conditioning regimens like BEAM<sup>6,7</sup>.

In autoimmune disorders, the reconstituted immune system following myeloablation/lymphoablation and autologous transplant yields qualitative changes in immune defects and modifications in adaptive immune responses. A large worldwide cohort showed that AHSCT can induce sustained remissions for more than 5 years in patients with severe autoimmune di-

**TABLE II. CONDITIONING REGIMEN (BEAM)**

	-6	-5	-4	-3	-2	-1	0
BCNU	x						
VP-16		x	x	x	x		
ARA-C		x	x	x	x		
Melph		x	x	x	x	x	
							BMT

BCNU-300mg/m<sup>2</sup>x1d; VP-16-200 mg/m<sup>2</sup> x4d; ARA-C-200 mg/m<sup>2</sup> 12/12 h x4d; Melphalan 140 mg/m<sup>2</sup> x1d  
BMT: bone marrow transplant

seases refractory to conventional therapy. The type of autoimmune disease, rather than transplant technique, was the most relevant determinant of outcome. Results improved with time and were associated with the transplant centers experience. Early identification of patients with autoimmune diseases unresponsive to conventional therapy is extremely important in order to provide timely eligibility criteria. Ongoing studies aim to use recently published clinical guidelines protocols of the EBMT, with centralized data collection<sup>6,7</sup>. Recently, it was presented the analysis of the (European ASTIS-trial), the first international, investigator-initiated, phase III HSCT trial in early diffuse cutaneous SSc. The data shows that, despite 10% treatment-related mortality, long term event-free survival and overall survival were better in the AHSTC group than in the group treated with intravenous pulse cyclophosphamide<sup>8</sup>.

With this case the authors would like to emphasize the use of AHSTC as a valid and successful treatment for refractory autoimmune diseases, and the importance of a timely referral.

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## Paradigm Shift IV

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