Stem Cell Transplantation (SCT) in Scleroderma

Yes or No?

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How to argue against those evidences?

Autologous non-myeloablative haemopoietic stem-cell transplantation compared with pulse cyclophosphamide once per month for systemic sclerosis (ASSIST): an open-label, randomised phase 2 trial


Lancet 2011; 378: 498-506

Figure 4: 2-year follow-up for all patients undergoing haemopoietic stem-cell transplantation. Data are for all patients who underwent transplantation and had at least 1 year of follow-up. PVC=forced vital capacity. DLCO=diffusing capacity of carbon monoxide.
SCT in Scleroderma? … Related questions

• What is Scleroderma?
• What are the goals of the treatment?
• Which patients should be treated?
• Should we use conventional treatments?
• Should we use innovative treatments?
• Which SCT should be used?
What is systemic sclerosis (« scleroderma »)?
«Scleroderma»

- «Auto-immune» disease; «connective tissue disease»
- NOT lupus
- Fibrosis, microangiopathy, auto-immunity

Wells A U et al. Rheumatology 2009;48:iii40-iii44
Heterogeneity and complexity

- Fibrosis
- Microangiopathy
- Immunity

ROS (Reactive Oxygen Species)
Heterogeneity and complexity

MICROANGIOPATHY

FIBROSIS

Gut
Heart

IMMUNITY

ROS

Skin sclerosis
Interstitial
Pneumonia

Anti-nuclear antibodies
anti- scl70
anti-centromere

Raynaud’s phenomenon
Digital ulcers
Telangiectasia
Pulmonary Arterial Hypertension
Renal crisis
Survival
Life-threatening Involvements

- Renal crisis
- Heart involvement
- Pulmonary hypertension
- Lung fibrosis

Mortality
Organ dysfunction and damages

- Chronic renal insufficiency
- Chronic Heart failure
- Lung fibrosis, respiratory insufficiency
- GI tract involvement
- Skin sclerosis, digital ulcers
- Musculoskeletal dysfunction, myopathies
- Mobility, autonomy

Morbidity
Health status, disability, quality of life

Measures of Systemic Sclerosis (Scleroderma)

Health Assessment Questionnaire (HAQ) and Scleroderma HAQ (SHAQ), Physician- and Patient-Rated Global Assessments, Symptom Burden Index (SBI), University of California, Los Angeles, Scleroderma Clinical Trials Consortium Gastrointestinal Scale (UCLA SCTC GIT) 2.0, Baseline Dyspnea Index (BDI) and Transition Dyspnea Index (TDI) (Mahler’s Index), Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR), and Raynaud’s Condition Score (RCS)

JANET POPE

Mouth handicap score (MHISS), Cochin Hand Functionnal Scale (CHFS)

Digital ulcers : Impact on survival

Strong implication of digital ulcers, interrelation with survival
Systemic sclerosis

- The clinical involvements and their impact are very heterogenous.
- The spectrum of the disease is really wide.
- It appears difficult to evaluate such a complex disease. Thus, how should we measure the effects of treatments?
Questions ....

• Which patients should be treated?

• Which treatments should be used?
What are the therapeutic options in systemic sclerosis in 2013?
2013 - Therapeutic strategies

« OLD SCHOOL »

Hematopoietic SCT
2013 - Therapeutic strategies

« OLD SCHOOL »
« OLD SCHOOL » strategy

- To suppress immune disorder
- To counteract each manifestation of scleroderma
- To adapt treatment according to patient’s status
« OLD SCHOOL » strategy

**IMMUNITY**

- **Immunosuppressive drugs**
  - Corticosteroids
    (be careful with renal crisis !)
  - Immunosuppressive drugs
    (Cyclophosphamide,
    Azathioprine,
    Methotrexate)
  - D-penicillamine
  - Biotherapies

**ORGAN DYSFUNCTION**

- **Symptomatic treatments**
  - Ppis, prokinetics, vasodilators, ...

- **Palliative treatments**
  - Lung transplantation
2013 - Therapeutic strategies

« OLD SCHOOL »

Adapt treatment to each patient
Combine therapies
2013 - Therapeutic strategies

Hematopoietic SCT
Hematopoietic SCT

- To suppress immune disorder
- To "reboot" the immune system...
- ASSIST, ASTIS, SCOT trials
- High toxicity and treatment-related mortality
- Kidneys, Heart
Hematopoietic SCT

The improvement is not so important

Variability of tested endpoints

And the disease does persist

Damages persist, Fibrosis persists

Relapses may occur

Burt et al. Lancet 2011
Secondary autoimmune diseases occurring after HSCT for an autoimmune disease: a retrospective study of the EBMT Autoimmune Disease Working Party

Thomas Daikeler, Myriam Labopin, Massimo Di Gioia, Mario Abinun, Tobias Alexander, Irene Miniati, Francesca Gualandi, Athanasios Fassas, Thierry Martin, Carl Philipp Schwarze, Nico Wulfraat, Maya Buch, Antonia Sampol, Enric Carreras, Benedicte Dubois, Bernd Gruhn, Tayfun Güngör, David Pohlreich, Annemie Schuerwegh, Emilian Snarski, John Snowden, Paul Veys, Anders Fasth, Stig Lenhoff, Chiara Messina, Jan Voswinkei, Manuela Badoglio, Jörg Henes, David Launay, Alan Tyndall, Eliane Gluckman, and Dominique Farge, on behalf of the EBMT Autoimmune Disease Working Party

Immune reconstitution? ... Are anti-Scl-70 Abs pathogenic?
American Scleroderma Stem Cell versus Immune Suppression Trial (ASSIST)

• 10 patients HSCT vs 9 patients 6-monthly pulses of i.v. cyclophosphamide 1000 mg/m²

• The study was stopped early for benefit

• no deaths (unusual):
  – sample size is small
  – follow-up is relatively short (12-24 months)
  – Selected patients have relatively mild disease

*Lancet 2011; 378: 498-506*
Autologous Stem cell Transplantation International Scleroderma trial (ASTIS)

• 79 patients: HSCT

Vs 77 patients: 12-monthly pulses of i.v. cyclophosphamide 750 mg/m²

• 40 deaths
  – 16 deaths in the SCT group, including 8 treatment related
  – 24 deaths in the control group. None from treatment-related causes

• Only smoking status affected outcome (event-free and overall survival +++).

_Blood_ 2012; **120**: 964 (abstr).
_Ann Rheum Dis_ 2012; **71** (suppl 3): 151 (abstr).
Cardiac « limits »

Cardiac involvement and treatment-related mortality after non-myeloablative haemopoietic stem-cell transplantation with unselected autologous peripheral blood for patients with systemic sclerosis: a retrospective analysis

Richard K Burt, Maria Carolina Oliveira, Sanjeev Shah, Daniela A Morales, Belinda Simoes, Mihai Gheorghiu, James Schroeder, Eric Ruderman, Dominic V Feng, Z Jessie Chai, Zora Majcenovic, Sandeep Jain, Amy Morgan, Francesca Milanetti, Xiaojiang Han, Branko Jovanovic, Irene B Helenowski, Julio Voltarelli

* Lancet 2013; 381: 1116–24

Reduced mortality: 8/90 died from disease-related causes and 5/90 (6%) patients died from treatment-related causes

4 treatment-related deaths occurred because of cardiovascular complications (1 constrictive pericarditis, 2 right heart failures without underlying infection, and 1 heart failure during mobilisation)

DLCO is affected by baseline cardiac function

>>> Appropriate cardiac assessment before HSCT?

not only echocardiogram… but also …confrontational right heart catheterisation, (with fluid challenge test) and cardiac MRI.

RISK OF THESE PROCEDURES
Renal « limits »: Acute Kidney Injury (AKI)

Three US clinical trials including SCOT – 91 Scleroderma patients

11 patients (12%) (8 autologous, 1 allogeneic, 1 pre-transplant, 1 given intravenous cyclophosphamide on transplant trial) developed AKI ... and 8 of 11 died

6 renal crisis; 3 AKI on scleroderma renal disease; 2 uncertain causes

>>> Limiting nephrotoxins
  cautious use of corticosteroids
  renal shielding during total body irradiation
  strict control of blood pressure and aggressive use of ACE-I
Selection of patients and new questions...

• High toxicity and treatment-related mortality
• Appropriate selection of patients

>>> HOW MANY PATIENTS WILL BE STILL ELIGIBLE?

• Treating less severe scleroderma patients?

>>> WILL HSCT REMAIN JUSTIFIED AND ETHICALLY CORRECT?
2013 available treatments

« OLD SCHOOL »
Adapt treatment to each patient
Combine therapies

Hematopoietic SCT
High toxicity
Treatment related mortality
Selection of patients

Balance benefit/risk and patient information
MICROANGIOPATHY

FIBROSIS

Gut
Heart

IMMUNITY

Skin sclerosis
Interstitial
Pneumonia

Anti-nuclear antibodies
anti- scl70,
anti-centromere

Raynaud’s
phenomenon
Digital ulcers
Telangiectasia
Arterial pulmonary
Hypertension
Renal crisis

ROS
2013 available treatments

FIBROSIS  →  IMMUNITY

MICROANGIOPATHY  →  IMMUNITY

ROS

?
Is autologous SCT in patients with Scleroderma justified?

It can be proposed in some selected patients,
Especially in the context of trials

HSCT Trials are justified +++
Are new treatments in patients with Scleroderma required?

YES
Next Therapeutic Approaches

FIBROSIS

MICROANGIOPATHY

ROS

IMMUNITY
Animal models of scleroderma

Bleomycin model

Hypochlorite (HOCl) - induced Murine Scleroderma

« Genetic » models

New Drugs

Mesenchymal Stem Cell therapy

New Targets

Global Approach
Animal models of scleroderma

HOCl - induced Murine Scleroderma

New Drugs

Mesenchymal Stem Cell therapy

New Targets

Global Approach
Selective Oxidation of DNA Topoisomerase 1 Induces Systemic Sclerosis in the Mouse

Amélie Servettaz, Claire Goulvestre, Niloufar Kavian, Carole Nicco, Philippe Guilpain, Christiane Chéreau, Vincent Vuiblet, Loïc Guillevin, Luc Mouthon, Bernard Weill, and Frédéric Batteux

HOCl - induced Murine Systemic sclerosis

Selective Oxidation of DNA Topoisomerase 1 Induces Systemic Sclerosis in the Mouse

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- Several oxidants tested
- Best results obtained with HOCl
- FIBROSIS
- MICROANBGIOPATHY
- DYSIMMUNITY
Animal models of scleroderma

New Drugs

HOCl - induced Murine Scleroderma

New Targets
New targets for pharmacological approaches

Targeting ADAM-17/Notch Signaling Abrogates the Development of Systemic Sclerosis in a Murine Model

Niloufar Kavian, Amélie Servettaz, Céline Mongaret, Andrew Wang, Carole Nico, Christiane Chéreau, Philippe Grange, Vincent Vuiblet, Philippe Birembaut, Marie-Danièle Diebold, Bernard Weill, Nicolas Dupin, and Frédéric Batteux

Targeting the Cannabinoid Pathway Limits the Development of Fibrosis and Autoimmunity in a Mouse Model of Systemic Sclerosis

The American Journal of Pathology, Vol. 177, No. 1, July 2010
Copyright © American Society for Investigative Pathology
DOI: 10.2353/ajpath.2010.090763

Amélie Servettaz, Niloufar Kavian, Carole Nico, Vanessa Deveaux, Christiane Chéreau, Andrew Wang, Andreas Zimmer, Sophie Lotersztajn, Bernard Weill, and Frédéric Batteux

The Organotelluride Catalyst (PHTE)$_2$NQ Prevents HOCI-Induced Systemic Sclerosis in Mouse

Wioleta K. Marut, Niloufar Kavian, Amélie Servettaz, Carole Nico, Lalla A. Ba, Mandy Duering, Christiane Chéreau, Claus Jacob, Bernard Weill, and Frédéric Batteux


Amelioration of Systemic Fibrosis in Mice by Angiotensin II Receptor Blockade

Wioleta Marut, Niloufar Kavian, Amélie Servettaz, Thong Hua-Huy, Carole Nico, Christiane Chéreau, Bernard Weill, Anh Tuan Dinh-Xuan, and Frédéric Batteux

Sunitinib Inhibits the Phosphorylation of Platelet-Derived Growth Factor Receptor β in the Skin of Mice With Scleroderma-like Features and Prevents the Development of the Disease

Niloufar Kavian, Amélie Servettaz, Wioleta Marut, Carole Nico, Christiane Chéreau, Bernard Weill, and Frédéric Batteux
Animal models of scleroderma

HOCl-induced Murine Scleroderma

Mesenchymal Stem Cell therapy
Animal models of scleroderma

- HOCl-induced Murine Scleroderma
- Mesenchymal Stem Cell therapy

- Weeks
  - 0
  - 2
  - 4
  - 6

- HOCl
- Phenotype
- Skin thickening
Animal models of scleroderma

HOCl - induced Murine Scleroderma

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Mesenchymal Stem Cell therapy

Weeks
0 2 4 6

HOCl

Phenotype

Skin thickening
Fibrosis and MSC: animal models

Models of fibrosis

Bleomycin-induced fibrosis
Acute injury and secondary fibrosis

BENEFICIAL EFFECT OF MSC

26;104(26):11002-7.
MSC and Scleroderma: preliminary results

- Improvement of d-SSc following allogenic MSC
  (Christopeit et al. Leukemia 2008)
- Revascularization of leg ischemia following autologous MSC
  (Giudicci et al. Ann Intern Med 2011)
- 5 cases of scleroderma treated with MSC
  (Keyszer et al. Arthritis 2011)
- Skin & ASC
  (Scuderi et al. Cell Transplant 2012)
- PHRC national France: 2011 D Farge Hôpital St Louis, AP-HP INSERM U 976
MSC phenotypes and properties in scleroderma

- « Impairment of Endothelial Cell Differentiation From Bone Marrow–Derived Mesenchymal Stem Cells » (Cipriani et al. Arthritis 2007)

- Immulogical properties (Larghero et al. ARD 2008)

- Altered phenotypes and hyperexpression of TGFbRII (Vanneaux et al. BMJ 2013)

- Senescent phenotype but preserved immunomodulation properties (Cipriani et al. Clin Exp Immunol 2013)
Conclusion

- HSCT : MAYBE (to be confirmed)
- MSC : to be studied

- A change in physicians’ mind is required...
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