COMMENTARY

Autologous hematopoietic cell transplantation for systemic sclerosis — a challenge for the Canadian health care system

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Systemic sclerosis is an uncommon disease (12 new cases per 1 000 000 per year in North America).[1] Treatment to date has been mostly symptomatic and supportive. Recently, high-dose immunosuppressive chemo/radiotherapy with autologous hematopoietic cell rescue (i.e., autologous hematopoietic cell transplantation), which has been used to treat lymphoma and myeloma since the 1980s, has been shown to be beneficial for patients with systemic sclerosis.[2] However, delivering autologous hematopoietic cell transplantation as the treatment of choice for select patients with systemic sclerosis poses several challenges for the Canadian health care system. Herein, we discuss systemic sclerosis, its treatments, and the challenges presented in treating conditions like systemic sclerosis with a new or experimental therapy in Canada.

Typical onset of systemic sclerosis occurs between 40 and 60 years of age. Systemic sclerosis includes primarily the skin, lungs and esophagus, although almost any organ can be involved. Pathogenesis is poorly understood but appears to involve abnormal behaviour of lymphocytes, endothelial cells and fibroblasts, presumably as a result of an autoimmune process. Unlike most rheumatologic disorders, including rheumatoid arthritis or lupus, which are not usually fatal, systemic sclerosis is associated with substantial mortality, in particular, for diffuse scleroderma with involvement of the kidneys, lungs or heart (more than 50% mortality within 10 years of disease onset),[3] or with rapid progression of skin thickening.[4]

Treatment of systemic sclerosis has been mostly symptomatic and supportive to date. Antihistamines may be used to treat pruritus. Calcium-channel blockers and angiotensin-converting-enzyme inhibitors may be used to treat Raynaud phenomenon and renal crisis, respectively. Endothelin-1 receptor antagonists, phosphodiesterase inhibitors or prostacyclin agonists have been used to manage pulmonary arterial hypertension. Proton pump inhibitors, prokinetic agents and antibiotics have been used for gastrointestinal problems.

Systemic immunosuppressive therapy with methotrexate, cyclophosphamide or mycophenolate mofetil has been shown to offer small improvement of skin tightness and stabilization or lung function, although these benefits may be only transient.[5]

KEY POINTS

- Systemic sclerosis is an uncommon and presumed autoimmune disease that is associated with high mortality.
- Mortality can be reduced and quality of life improved with high-dose immunosuppressive chemo/radiotherapy with autologous hematopoietic cell transplantation.
- Challenges within the Canadian health care system that need to be overcome to allow patients with systemic sclerosis to benefit from this new therapy include compartmentalization of health care into cancer versus noncancer treatment and provincial funding models, which make it difficult to concentrate experience at a few centres of excellence.

Allogeneic hematopoietic cell transplantation may result in long-term remission and possible cure of systemic sclerosis.[6–8] However, given its high risk of toxicity (graft-versus-host disease), the treatment remains experimental.

Autologous hematopoietic cell transplantation has been explored for systemic sclerosis since the 1990s. Single-arm (nonrandomized, phase I/II) studies (Appendix 1, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.161346/-/DC1) showed that autologous hematopoietic cell transplantation results in marked improvement of skin tightness and sustained stabilization of lung function in patients with expected deterioration of lung function.[9,10] Survival also appeared to be higher than expected based on previous studies of nontransplant patients. Based on these encouraging results, three randomized trials were conducted: a single-centre (Northwestern University) trial (Autologous Stem Cell Systemic Sclerosis Immune Suppression Trial, ASSIST), a multicentre European trial (Autologous Stem Cell Transplantation International Scleroderma, ASTIS) and a multicentre North American trial (Scleroderma: Cyclophosphamide or Transplantation, SCOT) (results are summarized in Appendix 1).

Lessons were learned from both nonrandomized and randomized studies: autologous hematopoietic cell transplantation is superior to conventional immunosuppressive therapy (low-dose intravenous cyclophosphamide given monthly) in patients with a disease duration of less than five years and involving the skin and lungs

(forced vital capacity 40%–80% predicted). The treatment may also be used in patients with severe skin involvement alone (a modified Rodnan skin score [mRSS] of 20 or more, a measure of the extent and severity of skin involvement). Benefits of autologous hematopoietic cell transplantation include improved survival, markedly improved mRSS, stabilization or small improvement of lung function and markedly improved quality of life. The risks are transplant-related mortality (about 3% to 10%) over a few years after the autologous hematopoietic cell transplantation, primarily because of heart or lung failure, or infections, and premature menopause/infertility (Appendix 1). Extrapolating from results for patients receiving autologous hematopoietic cell transplantation for lymphoma and myeloma, we expect late complications to include myelodysplasia/acute myeloid leukemia and solid tumours. Late complications may also include second autoimmune diseases, such as thyroiditis or immune cytopenia.[11]

The challenge of adopting autologous hematopoietic cell transplantation treatment for select Canadians with systemic sclerosis is the need to establish cross-specialty teams to treat a small number of eligible patients and to fund these teams and treatment. We offer several suggestions.

Comprehensive multidisciplinary teams that comprise rheumatologists, hematologists/oncologists, as well as respirologists, cardiologists, nephrologists, gastroenterologists and dermatologists, are needed to care for patients undergoing hematopoietic cell transplantation. These teams need to emerge and be supported. Because systemic sclerosis is uncommon, and only a fraction of patients with systemic sclerosis are indicated for autologous hematopoietic cell transplantation , it would be ideal to create only a few teams (centres of excellence), perhaps one in eastern and one in western Canada.

Although this model is supported by studies showing lower transplant-related mortality in centres with higher numbers of transplants for autoimmune diseases,[12,13] the provincial funding model that is used to support hematopoietic cell transplantation programs presents a challenge to developing these centres. The hospitals or cancer centres hosting the potential transplant programs of excellence may be reluctant or not allowed to accept patients from other provinces. Moreover, even within a province, oncology programs may be reluctant to take on care of these complex rheumatology patients without additional resources to manage them properly. We strongly urge more flexibility in allocation of budgets.

To further improve outcomes, transplants for systemic sclerosis should be performed ideally under the umbrella of international prospective trials. International trial investigators and funders typically select only experienced centres that perform a high volume of transplants for systemic sclerosis to participate in clinical trials. This further argues for the centralization of transplants in Canada for systemic sclerosis to only a few centres of excellence. This would also facilitate research on the pathogenesis of systemic sclerosis, and the mechanism of action of autologous hematopoietic cell transplantation .

Some provinces refer patients with systemic sclerosis who need hematopoietic cell transplantation to a centre of excellence in the United States. However, this has two disadvantages: it is expensive — the cost of hematopoietic cell transplantation in the US is at least twice as high as in Canada, and it deprives Canada of the opportunity to develop the expertise.

A solution may be found by developing multilateral agreements among academic medical centres and provincial health care authorities that would allow interprovincial exchange of patients with uncommon conditions. This would benefit patients, who could then be treated by an experienced team, and Canadian academic medicine, by fostering research and excellence.

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