

Autologous HSCT is efficacious, but can we make it safer?

Richard K. Burt and Dominique Farge

Autologous haematopoietic stem cell transplantation (HSCT) has proved efficacious in treating patients with systemic sclerosis, but different regimens have different associated toxicities and different effects on lung function. Through comparison of different clinical trials, we can learn how to improve the safety of HSCT.

Refers to Sullivan, K. M. et al. Myeloablative autologous stem-cell transplantation for severe scleroderma. *N. Engl. J. Med.* **378**, 35–47 (2018)

part attributed to a failure of private insurance reimbursement, the protocol design might have contributed to the slow enrolment as, for ethical reasons, both the ASSIST³ and ASTIS² trials allowed crossover to the HSCT arm, whereas the SCOT trial¹ did not.

The SCOT trial¹ was initially designed to be similar to the ASTIS trial² with regard to the control arm, enrolment criteria and the end point to enable comparison of these two different types of transplant regimen. In 2010, the primary end point of the SCOT trial¹ was changed to a non-clinical outcome, the global rank composite score (GRCS), which had never been vetted in an SSc trial. The GRCS is a hierarchical scoring system that compares each patient's relative scores for outcome variables, including death, EFS, FVC, the health assessment questionnaire-disability index and mRSS. The EFS did not significantly differ at 54 months between the HSCT and cyclophosphamide trial arms, whereas the new end point of GRCS showed a difference in favour of HSCT¹ (TABLE 1). At 72 months, the EFS also differed between the two groups in favour of HSCT. When the GRCS was broken into its component parts, the FVC did not improve significantly ($P=0.3$ by intention to treat and $P=0.5$ by per protocol), and malignancies were present in 9% of patients post-HSCT (two instances of myelodysplastic syndrome and one instance of medullary thyroid cancer)¹.

Following the initial ASSIST trial³, the ASSIST treatment regimen was used for 89 patients undergoing HSCT⁴ and resulted in improvement in mRSS, FVC and in all components of quality of life^{3,4} (Supplementary Table 1). Although the diffusing capacity for carbon monoxide (DLCO) did not show improvement from baseline following HSCT, DLCO did improve in a subset of patients who had normal pre-HSCT echocardiograms and electrocardiograms, emphasizing the under-appreciated importance of cardiac function for DLCO⁴. In the ASTIS trial², transplant related mortality was 10%, and was predominantly attributable to SSc-related cardiac dysfunction^{5,6}. However, by using a low dose of cyclophosphamide, the SCOT trial¹ was less affected by cardiac-related toxicity than the other trials. The safety of an intense cyclophosphamide regimen such as that used in the ASTIS trial² could be improved with a more extensive cardiac screening programme

The results from a new randomized trial, the SCOT trial¹, add to evidence from two previous trials (the ASTIS² and ASSIST³ trials) showing that autologous haematopoietic stem cell transplantation (HSCT) is superior to cyclophosphamide therapy for patients with systemic sclerosis (SSc). In these trials, the autologous haematopoietic stem cells had no direct therapeutic effect, but were infused to shorten cytopenia (non-myeloablative regimens) or to prevent long-term cytopenia (myeloablative regimens). Although HSCT has been proved to be efficacious for patients with SSc^{1–3}, concerns remain over the safety of the treatment, particularly with regard to cardiovascular risks and malignancies. Since toxicity and efficacy arise from the patients selected and the conditioning regimen used, physicians need to be aware of the different chemotherapy or radiotherapy regimens used in these trials (TABLE 1; Supplementary Table 1) to fully understand the subtle differences in results.

The ASTIS² and ASSIST³ trials used a non-myeloablative regimen of cyclophosphamide and rabbit anti-thymocyte globulin. The main difference between the treatments in the two studies was that in the ASSIST trial³, stem cells were mobilized before conditioning with 2 g/m² cyclophosphamide, and unmanipulated peripheral blood stem cells were infused, whereas in the ASTIS trial², stem cells were mobilized before conditioning with 4 g/m² cyclophosphamide, and peripheral blood

stem cells that had been purged of lymphocytes by selection of CD34⁺ cells *ex vivo* were infused. By contrast, the SCOT trial¹ used a lower dose of cyclophosphamide in the conditioning regimen (120 mg/kg instead of 200 mg/kg) than the ASTIS and ASSIST trials, but added total body irradiation, making the SCOT trial myeloablative.

The primary end point of the ASSIST trial³ was improvement in modified Rodnan skin score (mRSS) or in pulmonary forced vital capacity (FVC), and the design of this trial allowed patients in the cyclophosphamide arm who failed therapy to cross over to the HSCT arm after 1 year of therapy. Interim analysis revealed a statistically significant improvement for patients in the HSCT arm, whereas the majority of patients in the control arm worsened or crossed over to the HSCT arm³. By contrast, the ASTIS trial² had a primary end point of event-free survival (EFS), defined as the time from randomization until the occurrence of death or persistent major organ failure, and allowed crossover from the cyclophosphamide arm to the HSCT arm after 2 years of therapy. At 2 years, patients in the HSCT arm showed improvements in mRSS, FVC, total lung capacity and some components of quality of life² (Supplementary Table 1). EFS and overall survival rates were better for patients in the HSCT arm than for patients in the control arm². The SCOT trial¹ began recruiting in 2005, but was closed in 2011 owing to slow enrolment. Although in

Table 1 | Trials of autologous haematopoietic stem cell transplantation in systemic sclerosis

Trial	Patients treated with HSCT (n)	Regimen	End points	HSCT-related deaths	Incidence of cancer	Overall survival	Refs
ASSIST	10	Non-myeloablative • CYC 200 mg/kg • rATG 6.5 mg/kg	Clinical improvement (mRSS or FVC) ($P=0.00001$)	0%	0% (0 of 10)	100% (2 years)	³
ASSIST regimen	89	Non-myeloablative • CYC 200 mg/kg • rATG either 6.5 mg/kg or 4.5 mg/kg	• OS = 78% • RFS = 70% • mRSS ($P=0.0003$) • FVC ($P=0.004$)	6%	0% (0 of 89)	78% (5 years)	⁴
ASTIS	75	Non-myeloablative • CYC 200 mg/kg • rATG 7.5 mg/kg	• EFS ($P=0.006$) • mRSS ($P<0.001$) • FVC ($P=0.004$)	10%	1.3% (1 of 75)	• 82% (5 years) • OS ($P=0.002$)	²
SCOT	33	Myeloablative • TBI 800 cGy • CYC 120 mg/kg • eATG 90 mg/kg	EFS (2005–2010) • ITT ($P=0.06$) • PP ($P=0.02$) GRCS (after 2010) • ITT ($P=0.01$) • mRSS (ITT, $P=0.05$; PP, $P=0.01$) • FVC (ITT, $P=0.3$; PP, $P=0.5$)	6%	9% (3 of 33)	• 86% (54 months) • 54 months OS ($P=0.28$) • 72 months OS ($P=0.02$)	¹

CYC, cyclophosphamide; EFS, event-free survival; eATG, equine anti-thymocyte globulin; FVC, forced vital capacity; GRCS, global rank composite score; HSCT, haematopoietic stem cell transplantation; ITT, intention to treat; mRSS, modified Rodnan skin score; OS, overall survival; PP, per protocol; rATG, rabbit anti-thymocyte globulin; RFS, relapse-free survival; TBI, total body irradiation.

and by the exclusion of patients with SSC-related cardiac dysfunction. Recognizing this fact, subsequent to the design of these trials, recommendations suggested the use of a pre-transplant right heart catheterization protocol to exclude patients with a resting pulmonary artery systolic pressure of >40 mmHg (or >45 mmHg after a fluid challenge with 1 litre of intravenous saline) or a mean pulmonary artery pressure of >25 mmHg (or >30 mmHg after the same fluid challenge)⁷. A pre-HSCT cardiac MRI was also recommended to exclude patients with septal flattening^{5–7}. By adopting such a stringent cardiac screening programme, the ongoing European Society for Blood and Marrow Transplantation observational trial⁸ of 82 patients who have undergone HSCT has a transplant-related mortality of 6.1% at 2 years (D.F., unpublished observations).

Transplant-related mortality for the SCOT trial was equivalent to that for the ASSIST trial and lower than for the ASTIS trial (TABLE 1). However, the percentage of patients with major (grade 4) transplant-related adverse events was higher in the SCOT trial (85%)¹ compared with the ASTIS trial (37%)². In the SCOT trial, the three malignancies that occurred in the HSCT arm seemed to be related to the use of total body irradiation, and only one malignancy occurred in the control arm¹, as opposed to the incidence of malignancies in the ASTIS trial, in which one malignancy was reported in the HSCT arm and five malignancies were reported in the control arm². In addition, the total body irradiation-based regimen used in the SCOT trial did not improve pulmonary function in

patients¹, whereas the regimens used in the ASSIST and ASTIS trials improved both FVC and total lung capacity^{2,3}.

Overall, it seems that an intense cyclophosphamide regimen is not well tolerated by compromised hearts, whereas a total body irradiation-based regimen does not improve lung function and increases the risk of late-occurring cancer. Further trials of autologous HSCT for SSC are ongoing and non-myeloablative regimens are being developed that will hopefully be less toxic than those used to date. As our experience of using HSCT grows, HSCT regimens could be individualized according to a patient's cardiac function and the risk of renal crises. To minimize a 'centre effect', HSCT should be confined to centres that have expertise in what is an aggressive but effective treatment for patients with a lethal disease^{9,10}.

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Competing interests

The authors declare no competing interests.

SUPPLEMENTARY INFORMATION

See online article: Supplementary Table 1

ALL LINKS ARE ACTIVE IN THE ONLINE PDF

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Supplementary information

[Supplementary information S1](#) (table): Comparison of ASSIST, ASTIS and SCOT trials.

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