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New pathways in the pathogenesis of SSc

Haematopoietic stem cell transplantation for poor-prognosis systemic sclerosis

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Abstract

Haematopoietic stem cell transplantation (HSCT) following intensive immune suppression has been used in >2000 patients with severe autoimmune diseases for 18 years, including 300 with SSc. The concept is to profoundly reduce the bulk of auto-aggressive immune competent cells and then rescue the patient's ablated haematopoiesis via an autologous HSCT. An early analysis of uncontrolled phase I/II data suggested that approximately one-third of these achieved a substantial improvement, with a relapse rate of 25% and a treatment-related mortality ranging from 6% to 23% across different studies. These early results led to three prospective randomized controlled trials, two of which are completed, confirming that HSCT shows clear advantages over conventional immunosuppression, but with significant toxicity. In some patients, sustained complete normalization of skin changes, reversal of positive autoantibody status and withdrawal of immunosuppressive medication were observed. These results attest to the profound effects of HSCT.

Key words: haematopoietic stem cell transplantation, systemic sclerosis, remission induction.

REVIEW

Rheumatolozgy key messages

- Autologous stem cell transplantation is an effective treatment in selected patients with early dcSSc.
- SSc patients are at risk of serious toxicities including treatment-related death due to major organ involvement (notably heart, lungs, kidneys).
- Autologous stem cell transplantation in SSc should be performed by expert multidisciplinary teams in specialized transplant units.

Introduction

For decades, autologous haematopoietic stem cell transplantation (HSCT) has been used to re-establish normal haematopoiesis after major cytoreductive therapy for malignant disorders. This allows the administration of high-dose chemo- and/or radiotherapy since the HSCT reverses the otherwise severe aplasia that inevitably follows such treatment. Since the mid-1990s, following the publications of the successful outcome of the first transplanted SSc patients and spearheaded by the Autoimmune Diseases Working Party of the European Group for Blood and Marrow Transplantation, the EULAR and the International Stem Cell Project for Autoimmune Disease, the same approach has been used to treat selected patients with severe autoimmune disease (AD) [1–3].

From the outset it was recommended that only patients with a severe life- or organ-threatening AD should be considered for such a potentially toxic therapy. In addition, it was considered important that patients with end-stage or permanently severely damaged organs should not be transplanted, as the therapy was essentially anti-inflammatory and immunosuppressive rather than tissue regenerative. In SSc, reversal of fibrosis or vascular pathology was not expected. As the programme progressed, some gratifyingly positive results regarding regression of fibrosis and de-remodelling of the vasculature were observed in transplanted SSc patients, reminding us that the complexity of the cellular players in the three-dimensional niche of AD pathology is far from fully understood.

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HSCT for SSc

At the inception of the programme, biologics had not yet become available and every AD subgroup had many cases severe enough to be considered for HSCT, notably those who had failed conventional therapy and had active inflammatory disease, which if slowed or arrested would still result in a significant quality of life. An early analysis of the phase I/ II data showed that significant numbers of patients in all AD subgroups had benefited from autologous HSCT, with the highest sustained responses seen in SSc [3]. Less toxic and effective therapeutic alternatives have evolved for many ADs, reducing the need for HSCT in diseases such as RA and JIA. In contrast, SSc remains a difficult-to-treat condition despite the therapeutic use of ACE inhibitors for scleroderma renal crisis, endothelin-1 receptor antagonists for pulmonary arterial hypertension (PAH) and immunosuppressants such as MMF [4, 5]. In addition, predictors of poor outcome such as PAH, reduced diffusion capacity of the lung for carbon monoxide (DLCO) and functional status are becoming better defined [6]. However, HSCT in SSc was associated with higher toxicity, not only related to known risk factors for HSCT such as the age of the patient, time from diagnosis to transplant, co-morbidity and regimen intensity, but also SSc-associated co-morbidities such as severe PAH, reduced left ventricular ejection fraction (LVEF) or ventricular tachyarrhythmias [7].

Which transplant regimen is best?

In the absence of adequate data, many theoretical arguments were put forward to support allogeneic HSCT as the best option for inducing remission. The main reason proposed was the need to replace an auto-aggressive corrupted immune system with a healthy one. While this made some sense, there were facts and findings that challenged this. First, the concordance rate of SSc (and most other ADs) in monozygotic twins is relatively low, indicating that stem cells and immune cells from genetically predisposed individuals are not necessarily programmed to become auto-aggressive [8]. In addition, there were case reports of RA patients receiving allogeneic HSCT for aplastic anaemia in whom later relapse was associated with full chimerism of the previously healthy immune competent cells [9]. More importantly, allogeneic HSCT is associated with graft-*vs*-host disease, a complication not present in the autologous situation. This unintended consequence was indeed observed in one of two SSc patients treated with allogeneic HSCT, with the other patient reportedly having improved significantly [10]. In an analysis of 38 allogeneic transplants in 35 patients with various haematological/non-haematological ADs (none with SSc), treatment-related mortality (TRM) was 22.1% [11]. This high percentage must of course be interpreted in the context of the severity of the disease in these patients, which in the absence of data from a control group is a daunting task.

The case for autologous HSCT was sealed, however, when studies in animal models of AD demonstrated that not only allogeneic but also autologous HSCT could induce sustained remission [12]. Of note, none of these included animal models of SSc. Further discussions centred around the issue of the degree of intensity of the conditioning regimens required; in other words, to what extend should one try to eliminate the host's autoreactive immune competent cells as opposed to inducing regulation?

At each step of autologous HSCT it is possible to employ varying intensities of treatment, including the complete omission of graft manipulation or purging. This does not exclude removal of unwanted immune competent lymphocytes since, on reinfusion after conditioning, the anti-thymocyte globulin (ATG) lyses many of these *in vivo*. The result is a less prolonged period of immunosuppression than that seen by extensive *ex vivo* purging. In the absence of data from comparative trials, a limited number of protocols were pursued, with a suggestion later that the intermediate intensity regimen offered the best compromise between efficacy and toxicity [13]. A typical intermediate intensity regimen is mobilization with CYC $2 \times 1\,g/m^2$ body area and G-CSF, *ex vivo* CD34 selection of the graft and conditioning with CYC 200 mg/kg body weight combined with rabbit ATG 7.5 mg/kg body weight, a regimen used in the Autologous Stem Cell Transplantation International Scleroderma (ASTIS) trial (see below). The available data do not allow conclusions as to which autologous transplant regimen is best since head-to-head studies have not been done, but the recently updated guidelines reaffirm the preference for autologous as opposed to allogeneic HSCT [14].

Treatment-related mortality of HSCT in SSc—results from pilot studies

Whatever the choice of regimen intensity, it is clear that even autologous HSCT protocols carry a finite TRM, which in all but the smallest studies in SSc patients has ranged from 6% to 17% with non-irradiation-based treatment protocols (Table 1) [15]. In a North American pilot study, 8 of 34 SSc patients (23%) died from treatment-related complications following mobilization with G-CSF, subsequent CD34 selection of the graft and conditioning with high-dose CYC, ATG and fractionated total body irradiation (TBI) [16]. The US investigator group amended their protocol to include lung and kidney shielding to minimize the risk of organ toxicity from TBI and continued to refine their protocol as a basis for the Scleroderma: Cyclophosphamide or Transplantation (SCOT) trial (see below). In comparison with transplant results in other ADs, TRM in SSc patients has been relatively high, and this has been ascribed to the severity of disease and the presence of major organ dysfunction in transplanted SSc patients [21]. In general, TRM in HSCT settings is related to the transplant regimen used (e.g. cardiotoxocity from high-dose CYC), patient selection and centre effect. It has proved very difficult to extract meaningful comparative information on this from the different pilot studies and registry analyses published to date. Interpretation is

TABLE 1 HSCT-related mortality in SSc studies and trials with 10 or more transplanted patients

Reference	Treatment-related death, *n/N* (%)
Nash *et al.* [16]	8/34 (23.6)
Binks *et al.* [7]	7/41 (17.1)
Henes *et al.* [17]	3/26 (11.6)
van Laar *et al.* [18]	8/75 (10.7)
Farge *et al.* [19]	1/11 (9.1)
Burt *et al.* [20]	5/90 (5.6)

hampered by the use of different definitions for TRM, the lack of autopsy results and the absence of independent data monitoring committees for adjudication of causes of death.

Outcome measurement in SSc

Currently no internationally agreed criteria exist for remission in SSc, although international collaboration is ongoing regarding outcome measurement in SSc clinical trials [24]. It would seem reasonable to assume that if the clinical activity score is minimal and vital organ function stabilizes in a patient not receiving significant immunosuppressive agents, then for all intents and purposes a remission can be assumed [25]. It is important to note that the diffuse cutaneous form of SSc often shows a spontaneous time-dependent improvement in skin thickness, measured by the modified Rodnan skin score (mRSS). This may occur in approximately two-thirds of patients and is associated with improved survival [26]. This should be taken into account in any clinical trial using the mRSS as an outcome measure. In addition, improvement of skin thickening on the chest wall will be reflected by an improvement in the forced vital capacity, but not necessarily improved interstitial lung disease. It was observed early in the AD transplant programme that a number of patients relapse after an initial improvement following HSCT. In contrast to malignancies, where the term relapse has been defined, no accepted operational definitions are available for rheumatological diseases such as SSc. The difficulties with defining such outcomes are not unique to SSc, as illustrated by the lack of consensus on the meaning of flare in RA. In contrast, one can envisage that the stark improvements of disease activity in transplanted SSc patients may provide a unique opportunity to test or validate new constructs such as remission.

Outcomes in SSc following autologous HSCT

Early in the international AD transplant programme, case reports and small series were published suggesting significant improvement in both survival and morbidity following autologous HSCT. The first published case of a patient receiving an HSCT as specific treatment for an AD was a case of SSc with PAH (mean pulmonary artery pressure 50 mmHg) in whom a sustained improvement in both mean pulmonary artery pressure (37 mmHg) and general clinical state was observed [1]. From early registry data in 41 SSc patients, approximately one-third of SSc patients achieved a sustained remission, with a TRM of 17% [7]. This later fell to 8.7% through further experience and increased patient numbers [27]. Similar positive outcomes were observed also in the USA [16]. As mentioned above, pulmonary and renal toxicity related to TBI was observed in the first group of patients, which was later mostly abrogated by selective lung and kidney shielding.

In general, all involved groups experienced a learning curve regarding toxicity. Examples include the following: rapid fluid and electrolyte shifts and glucocorticoid infusions are risk factors for scleroderma renal crisis and tight control of fluid status and prophylactic angiotensin-converting enzyme (ACE) inhibition has been used to mitigate this in the ASTIS trial; comprehensive pre-transplant cardiac screening and, when indicated (ventricular tachyarrhythmias), implantation of a defibrillating pacemaker [28]; and the use of adequate glucocorticoid therapy during the ATG infusion to reduce cytokine storm events.

In most studies done to date, HSCT consistently led to unprecedented and rapid improvements in mRSS and functional capacity (HAQ Disability Index), and stabilization of organ function [LVEF, vital capacity (VC), DLCO, creatinine clearance]. Furthermore, encouraging data emerged regarding changes in collagen deposition in involved skin and improved microcirculation in skin and nail folds [29–32]. The mechanism for such profound and mostly sustained changes remains elusive, since none of the individual agents used in the mobilization and conditioning components of the HSCT regimen are active directly on collagen-producing myofibroblasts, angiogenesis-competent endothelial cells and pericytes. It is conceivable, however, that the anti-fibrotic effects of HSCT result from disruption of the crosstalk between immune cells and stromal cells (reviewed in Hügle and van Laar [33]).

The encouraging data from registry studies and phase I/II trials were considered sufficient to justify confirmatory randomized controlled trials (RCTs). It was important to establish whether HSCT impacted on clinically meaningful endpoints such as event-free survival and organ damage rather than just changes in skin score and organ function when compared head-to-head with standard chemotherapy. In addition, such trials also provide material and data for mechanistic studies to try to understand how the remissions observed were achieved in order to fine tune future studies to maximize benefit and reduce risk.

Prospective randomized trials

To date, three prospective RCTs have been completed with HSCT in SSc (Table 2). Due to the profound clinical effects of HSCT, blinding of clinicians, patients and assessors for outcome measures is not possible. This should be taken into account when interpreting the effects on

Table 2 Main eligibility criteria of HSCT randomized controlled trials in SSc

Trial	ASTIS	ASSIST	SCOT
Main inclusion criteria	16–65 years of age Diffuse SSc: ⩽2 years since development of first sign of skin thickening, mRSS ⩾20, involvement of trunk, ESR >25 mm/h and/or Hb <11 g/dl; or ⩽4 years since development of first sign of skin thickening, mRSS ⩾15, major organ involvement[a]	<60 years of age Diffuse SSc: cutaneous involvement proximal to the elbow or knee, mRSS >14[b], internal organ involvement[c], disease duration ⩽4 years	<65 years of age Diffuse SSc: mRSS ⩾16, sSignificant visceral organ involvement[d], disease duration ⩽4 years
Main exclusion criteria	Mean PAP >50 mmHg, DLCO <40%, respiratory failure[e], LVEF by MUGA or cardiac echo <45%, creatinine clearance <40 ml/min, prior treatment with TLI, TBI or alkylating agents including CYC (total cumulative i.v. dose of >5 g, or >3 months oral up to 2 mg/kg body weight)	Mean PAP >25 mmHg or PASP >40 mmHg, TLC <45% (predicted), LVEF <40%, serum creatinine >177 μmol/l, prior treatment with >6 i.v. injection of CYC	DLCO <45% or using supplemental oxygen at rest; severe heart, liver or kidney impairment; active GAVE; prior treatment with i.v. CYC for >6 months or a total cumulative i.v. dose >3 g/m^2; oral CYC for >4 months, regardless of dose; or a combination of oral and i.v. CYC for >6 months, independent of dose

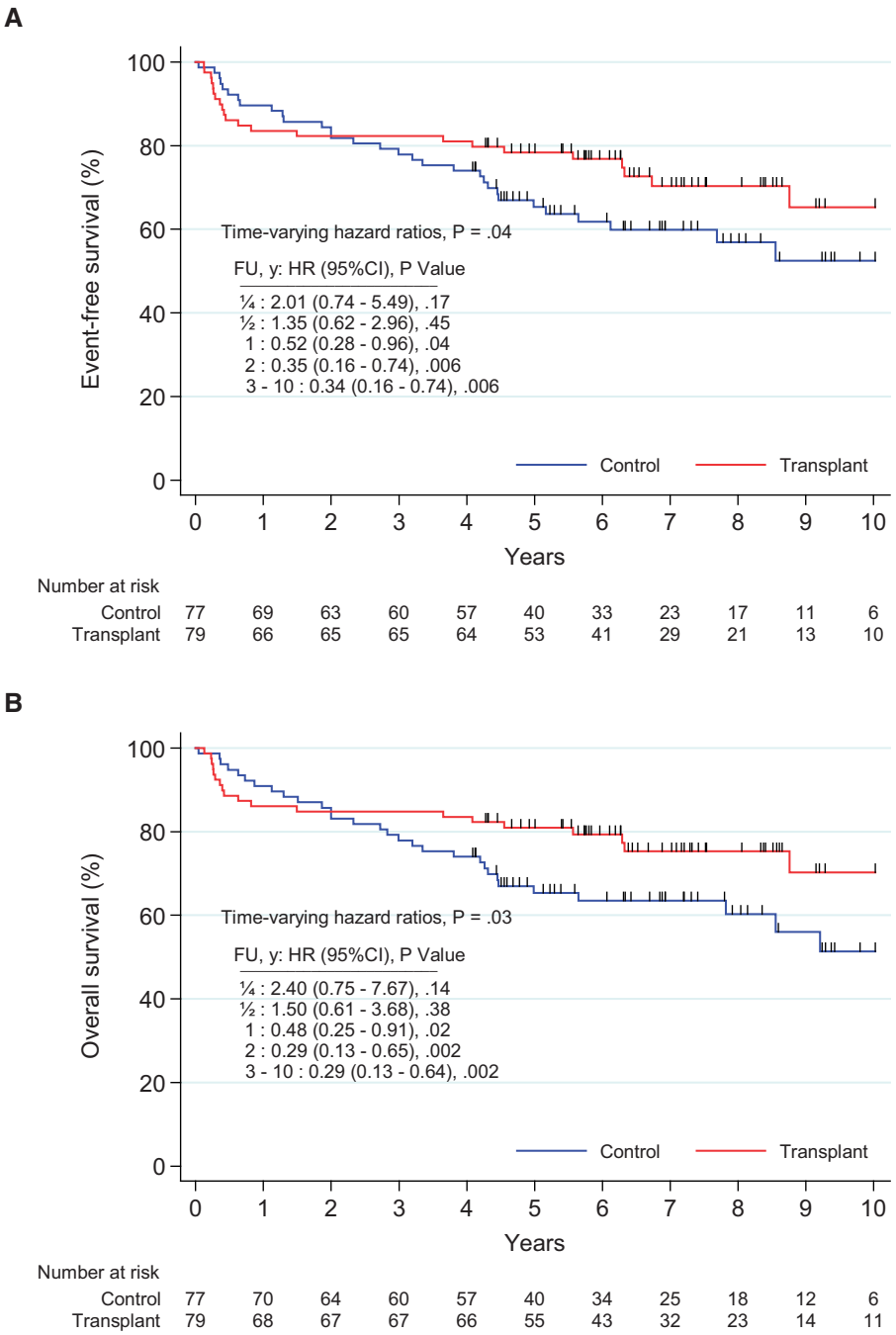
[a]Major organ involvement defined as involvement of lung, kidney or heart. [b]In cases of restricted skin involvement (mRSS <14), patients were eligible only if they had coexistent pulmonary involvement. [c]Internal organ involvement was defined as involvement of lung, heart or gastrointestinal tract. [d]Significant visceral organ involvement was defined as involvement of lung, heart or kidney. [e]Respiratory failure was defined by resting arterial oxygen tension (PaO_2) <8 kPa (<60 mmHg) and/or resting arterial carbon dioxide tension ($PaCO_2$) >6.7 kPa (>50 mmHg) without oxygen supply. DLCO: diffusion capacity of the lung for carbon monoxide; GAVE: gastric antral vascular ectasia; Hb: haemoglobin; LVEF: left ventricular ejection fraction; mRSS: modified Rodnan skin score; MUGA: multiple gated acquisition scan; PAP: pulmonary artery pressure; PASP: pulmonary artery systolic pressure; TBI: total body irradiation; TLC: total lung capacity; TLI: total lymphoid irradiation.

subjective measures such as skin thickening and patient-reported outcomes. Nevertheless, the results from the two completed phase III RCTs to date are entirely consistent with the published data from pilot studies, registry analyses and a small phase II RCT.

The ASSIST trial was the first published randomized trial to demonstrate superior efficacy of HSCT *vs* 6 monthly pulses of CYC (1 g/m^2) on skin thickness, lung function and quality of life [34]. This North American single-centre phase II trial involved only 19 patients, 10 of whom were randomized to HSCT and 9 to pulse CYC. Crossing over was allowed, and eight of nine control patients received HSCT because of an unsatisfactory response to pulse CYC. Baseline characteristics of the two groups differed slightly due to the small sample size, but the authors mentioned that this had not affected the outcome of the trial. Also, the number and dosing of CYC in the control group were lower than used in clinical practice, which may have contributed to the observed substantial differential effect of the two interventions. Importantly, no patient died during the study and serious toxicities were uncommon. While these favourable toxicity data could be testament to the experience of the clinical team, it cannot be ruled out that these are chance findings related to the small sample size and the relatively short observation period (up to 2 years after HSCT). Furthermore, the trial was stopped early for benefit, an important caveat since such trials tend to overestimate clinical efficacy [22].

The first completed and published phase III randomized trial in the field was the ASTIS trial [18]. This international clinical trial involved 156 patients with poor-prognosis early dcSSc enrolled via 29 centres (28 in Europe and 1 in Canada) from 2001 to 2009. Patients were randomized to either HSCT or 12 monthly pulses of CYC (750 mg/m^2). The trial, with a median follow-up of 5.8 years, showed that HSCT significantly prolonged event-free survival (the primary endpoint), defined as overall survival minus the occurrence of major organ failure of heart, lungs or kidneys according to pre-specified criteria, and overall survival (Fig. 1) [31]. Fifty-three events occurred: 22 in the HSCT group (19 deaths and 3 irreversible organ failures) and 31 in the control group (23 deaths and 8 irreversible organ failures, 7 of whom died later). Secondary endpoints defined as the change in the first 2 years of mRSS, HAQ, EuroQoL, or the 36-item Short Form Health Survey were also significantly better in the HSCT group. No significant changes were seen for LVEF or DLCO, but a modest but statistically significant decrease in creatinine clearance and an increase in FVC/VC was seen in the HSCT group. In terms of toxicity, more grade 3 and 4 serious adverse events were documented in the HSCT group, mainly related to febrile neutropenia. Also, more viral infections occurred after HSCT, including two cases of EBV-related post-transplant lymphoproliferative disease, one of which was successfully treated with rituximab while the other had a fatal outcome. TRM in the HSCT

Fig. 1 Event-free survival and overall survival over a 10 year follow-up period



(**A**) Kaplan–Meier curves for event-free survival. (**B**) Kaplan–Meier curves for overall survival. Hazard ratios and 95% CIs were calculated by Cox regression. Hazard ratios were time varying. Figure adapted from van Laar JM *et al*. [18].

group was 10.1%, which was mainly accounted for by cardiopulmonary insufficiency during conditioning, possibly from the administration of ATG and the resulting cytokine release syndrome. Every case was thoroughly reviewed by an independent data monitoring committee, who adjudicated each cause of death as being either treatment related or due to disease progression or an unrelated cause. No patient in the control group died from treatment-related complications, and most fatalities were due to disease progression. A *post hoc* analysis revealed

that seven of eight cases of TRM in the HSCT group occurred in ever smokers, while non-smokers enjoyed the greatest survival benefit after HSCT. The TRM in the ASTIS trial is in the range of TRMs reported in the pilot studies and should be interpreted in the context of disease severity. It is conceivable that HSCT in less advanced disease will prove safer, but this remains to be demonstrated. The problem of cytokine release syndrome during HSCT is well recognized and new treatment options are being tested [35].

Whatever one reads into the aforementioned results, it must be remembered that the ASTIS trial was designed as a proof-of-principle study, which for the first time demonstrated that intensive immunosuppressive treatment in early dcSSc fundamentally alters the long-term outcome of patients with poor-prognosis SSc. Furthermore, its results suggested that patients can be stratified on the basis of a simple feature, such as smoking status, into those at risk of serious toxicity and TRM (ever smokers) and those with a high probability of enjoying a favourable outcome (non-smokers). However, these findings from *post hoc* analyses need to be confirmed in other trials or large registry studies before policy decisions can be made with some confidence. At present, it is unclear how smoking status affects the outcome of HSCT, but the observation of a link between smoking status and outcome after HSCT in SSc is consistent with similar results in other transplant settings [36].

The North American SCOT trial used eligibility criteria broadly similar to those of the ASTIS trial and an almost identical control treatment, only differing in the specifics of the HSCT regimen (with TBI) and the definition of endpoints. Accrual in the SCOT trial has been completed but the results have not yet been published. The similarities between the ASTIS and SCOT trials will allow comparative analyses that may help to identify the optimal patient profile for HSCT and determine whether details of transplant regimens matter. The patient populations in both trials are relatively homogeneous in terms of the extent of skin thickening, organ involvement and disease duration, and the intensive screening procedures have revealed that some manifestations previously thought to be rare, such as gastric antral vascular ectasia, are actually quite common in this particular subgroup [37].

Long-term follow-up of transplanted SSc patients is essential to identify known late sequelae of HSCT, such as secondary AD and malignancy [38]. HSCT is an expensive treatment, and health care providers and patients have a right to be informed about the pros and cons of HSCT as opposed to conventional immunosuppression. In this context, it is worth noting that the literature on the long-term benefits and adverse effects of conventional immunosuppressive treatments such as MMF and MTX in SSc patients is scarce, if existent at all. As yet there has not been a breakthrough with biologic treatment in SSc, although some positive results have been recently reported with B cell depletion [23, 39]. While encouraging, conclusive evidence of the efficacy of biologics can only be obtained via prospective RCTs, because of the heterogeneity of the disease and its unpredictable disease course.

Conclusion

There is now ample evidence that HSCT can result in significant improvement of skin thickness and functional ability in SSc, while the recently completed ASTIS trial demonstrated that HSCT can also prolong survival in selected patients with dcSSc when compared with i.v. pulse CYC. Smoking status affected outcome after HSCT in the ASTIS trial. Further analyses and studies are needed to determine whether HSCT should be offered as first-line chemotherapy or as salvage treatment for those not responding to i.v. pulse CYC. HSCT in SSc is associated with serious toxicities that may be fatal. Some investigators advocate the use of intravascular fluid challenge of the heart to detect subclinical cardiac involvement and exclude those allegedly at risk of complications from conditioning, including hyperhydration, but this is not standard practice in most transplant centres [20]. A thorough cardiac workup is necessary though, in accordance with published guidelines [40]. The prophylactic use of ACE inhibitors in HSCT patients, as recommended in the ASTIS trial, is an area of controversy since a recent study revealed an association between prior use of ACE inhibitors and death from scleroderma renal crisis [41]. The number of cases of scleroderma renal crisis in the ASTIS trial was low, however, thus not substantiating the concerns raised. Further studies are needed to optimize patient selection so as to reduce toxicity and define those patients most likely to benefit from the procedure. This requires identification of poor-prognosis SSc patients at an early stage before advanced and irreversible organ involvement has occurred. While major progress has been made to delineate predictive features of poor outcome on a patient population level, our ability to do so on an individual patient level is still imperfect [42, 43]. Given the low prevalence of severe SSc and the complexities of HSCT in these patients, HSCT is probably best performed in specialist stem cell transplant units with access to multidisciplinary teams that include not only haematologists, but also rheumatologists with experience in the management of severe SSc, cardiologists and pulmonologists.

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