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ARTICLE

Long term outcomes of the French ASTIS systemic sclerosis cohort using the global rank composite score

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Abstract

Two randomised trials (ASTIS, SCOT) of Autologous Hematopoietic Stem Cell Transplantation (AHSCT) versus monthly Cyclophosphamide for severe Systemic Sclerosis (SSc) patients used similar inclusion criteria, but different primary endpoints: event-free-survival (EFS) at 24 months in ASTIS versus the global rank composite score (GRCS) at 54 months in SCOT. Here we analysed the French ASTIS cohort ($n = 49$) outcome using the same GRCS endpoint as reported in SCOT. All patients, randomised to AHSCT ($n = 26$) or Cyclophosphamide ($n = 23$), were evaluated for the non-parametric GRCS endpoint based on: death, EFS, forced vital capacity (FVC), Health Assessment Questionnaire Disability Index (HAQ-DI) and modified Rodnan skin score (mRSS) at 60 months. Secondary endpoints were: EFS, overall survival (OS), HAQ DI and organ status. In intention-to-treat analysis, the GRCS demonstrated superiority for AHSCT (median: 9 versus −19, $p = 0.018$), mRSS (Δ mRSS: −16 versus −9, $p = 0.02$), and HAQ-DI (ΔHAQ-DI: −0.89 versus −0.2, $p = 0.05$) with no significant difference in OS, EFS, lung, heart and kidney function between the groups. In conclusion, this study demonstrates long term benefits of non-myeloablative AHSCT when assessed by the five longitudinal measures within GRCS affording direct primary endpoint comparison between ASTIS and SCOT.

Introduction

Systemic Sclerosis (SSc) is a rare and severe chronic systemic autoimmune disease with high disease-related morbidity and a standardised mortality ratio above 3.5 compared to general population [1]. It is characterised by early endothelial vascular damage, activation of the immune response and progressive fibrosis within the skin and internal organs (lungs, gastrointestinal tract, heart and kidneys) [2]. Rapidly progressive diffuse SSc (dcSSc), within the first 5 years of disease onset, is a life-threatening condition, with a 3–5 years survival between 50 and 70% [1]. The main causes of death are cardiac and pulmonary related [1, 3].

Several risk factors were shown to affect survival in SSc patients once the diagnosis is established on the first non-Raynaud phenomenon, specifically the presence of diffuse skin fibrosis [4] as measured with modified Rodnan skin

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score (mRSS, range 0–51) [5], altered functional status assessed using the self reported Health Assessment Questionnaire (HAQ-DI) [6, 7], elevated C-reactive protein levels, altered renal function or scleroderma renal crisis, cardiac involvement with altered ventricular ejection fraction on echocardiography or earlier detection on magnetic resonance imaging [8], lung involvement with reduced forced vital capacity (FVC) or diffusion capacity for carbon monoxide (DLCO) on lung function tests, interstitial lung disease (ILD) on Chest X-ray or CT-scan, pulmonary arterial hypertension [9].

Three successive randomised controlled trial (RCT), ASSIST (American Scleroderma Stem cell versus Immune Suppression Trial) in 2011 [10] and ASTIS (Autologous Stem cell Transplantation International Scleroderma trial) in 2014 [11] both using non-myeloablative regimen and SCOT (Scleroderma: Cyclophosphamide Or Transplantation) in 2018 [12] using myeloablative conditioning, demonstrated the superiority of Autologous Hematopoietic Stem Cell Transplantation (AHSCT) compared to cyclophosphamide intravenous (iv) pulses. ASSIST and ASTIS utilised a non-myeloablative regimen of cyclophosphamide (200 mg/kg total dose) and rabbit antithymocyte globulin (rATG) and the main difference between the two studies was that ASSIST mobilised stem cells with 2 g/m^2 cyclophosphamide and infused unmanipulated peripheral blood stem cells (PBSC), while ASTIS mobilised stem cells with 4 g/m^2 cyclophosphamide and infused CD34+ selected PBSC. The SCOT trial used no cyclophosphamide with only GCS-F for mobilisation and a lower dose of cyclophosphamide (120 mg/kg total dose) for conditioning plus total body irradiation (800 cGy/4 fractions over 2 days/200 cGy to lungs and kidneys with shielding) which induces myeloablation. AHSCT for early severe dcSSc patients is now recommended with a grade I level of evidence by the European Bone Marrow Transplant Association (EBMT) [13], and by the American Rheumatism Association (ACR) and The European League Against Rheumatism [14] and the American Society for Transplantation and Cellular Therapy [15], with increased transplant activity reported to the EBMT registry and worldwide over the last decade.

ASTIS [11] and SCOT [12] RCT were designed using similar inclusion criteria and controls arms but different conditioning regimen. Both trials reported significant improvement in patients overall survival (OS) until at least 54 months after transplant. However, ASTIS and SCOT used different primary endpoints, respectively defined by the event-free survival (EFS) at 24 months in ASTIS and the global rank composite score (GRCS) at 54 months in SCOT. The GRCS is an analytic tool based on a composite score, which was used for the first time in this setting to assess SSc patients.

We, therefore, designed the present study using both the GRCS and the EFS to evaluate the long-term efficacy of non-myeloablative AHSCT versus Cyclophosphamide in the French subgroup of all ASTIS patients, who underwent extended follow-up until 60 months after randomisation in the ASTIS trial.

Material and methods

Study population

All consecutive French patients included in the multicenter open-label ASTIS trial, randomised (1:1) to receive AHSCT or Cyclophosphamide. Inclusion and exclusion criteria were previously published in ASTIS trial [11].

Randomisation

In the open-label ASTIS trial [11], a specific computer programme was used for centralised randomisation by block (2, 4 or 6), with stratification by centre, age (≤ or >40 years) and disease duration (< or ≥2 years), including a minimisation procedure (with 25% more chance of being assigned to the non-optimal group). Crossing-over was allowed after 24 months of follow-up. Stratification by centre ensured balanced between the groups among the French patients initially enroled, randomised and followed in ASTIS until October 31, 2013. All French ASTIS patients were subsequently included in the prospective Maladies Auto-Immunes et Thérapie Cellulaire (MATHEC) cohort for extended follow-up, which consisted of yearly prospective, standardised evaluations until 60 months after randomisation or their last visit.

Ethical considerations

All patients provided written informed consent for participation in ASTIS and post-transplant prospective follow-up and data collection in the St-Louis Center of reference ASTIS-MATHEC cohort. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Data collection

Demographic variables were recorded at baseline: age, sex, smoking and geographic origin, disease duration since first non-Raynaud symptoms, previous total dose of iv Cyclophosphamide, presence of antinuclear, anti-topoisomerase (anti-Scl70) or anticentromere autoantibodies, body mass index and standard biological data, including urinary analysis. Results from functional and physical evaluation were

collected at baseline and at least yearly after treatment for all patients, with repeated assessment until 60 months follow-up of: mRSS and HAQ-DI scores; pulmonary involvement using the percentage of predicted value (%) for FVC and DLCO on lung function tests, blood gaz analysis and presence of ILD or fibrosis on chest x-rays or high resolution computed tomography scan; cardiac involvement based on abnormalities on electrocardiography, or systolic pulmonary artery pressure and left ventricular ejection fraction (LVEF%) on echocardiography; kidney involvement using serum creatinine values.

Intervention

As previously reported in the ASTIS trial [11], patients received either (a) AHSCT after PBSC mobilisation with 4 g/m^2 cyclophosphamide and a non-myeloablative regimen conditioning (cyclophosphamide 200 mg/kg total dose) with rATG (Genzyme) and reinfusion of CD34 + PBSC, or (b) 12 intravenous monthly pulses of Cyclophosphamide (750 mg/m²).

Endpoints

The primary endpoint was the GRCS at 60 months, comparing participants with each other to reflect the order of each subject relative to all other cohort subjects, based on a hierarchy of outcomes: death, EFS as survival without respiratory event (defined by decrease of >30% in DLCO or a decrease of >20% in FVC measured at baseline or resting arterial pO2 < 60 mmHg or pCO2 > 50 mmHg without supplemental oxygen), renal event (defined by chronic dialysis >6 months or renal transplantation), or cardiac event (defined by clinical dyspnoea New York Class III or IV, or LVEF < 30% by echocardiogram), improvement or worsening evolution from baseline of FVC (if respective increase or decrease by at least 10%), HAQ-DI (if respective decrease or increase by at least 0.4) and mRSS (if respective decrease or increase by at least 25%). This allowed to assign a "pairwise comparison score" of 1 (better off), 0 (no different), or −1 (worse off), which we then summed (n-1 pairwise comparison with n being the number of subjects) to yield the GRCS for each subject [12]. Secondary endpoints were: EFS, OS, mRSS, FVC, DLCO, LVEF, serum creatinine and HAQ-DI.

Statistical analysis

We described and compared the characteristics of the two groups using non-parametric Wilcoxon test for quantitative variables if their distribution was not normal, student's t-test for normal distribution, and Fisher's exact test for categorical variables. All analyses were performed by intention-to-treat (ITT). The GRCS score was calculated at 60 months using the SCOT methodology, which excluded patients lost to follow-up. The non-parametric Wilcoxon test was used to compare the GRCS scores between AHSCT and cyclophopshamide groups. To compare EFS and OS between the two groups, we performed survival analysis using Kaplan Meier (KM) curves with log rank tests and Cox proportional hazards models to generate hazard ratios. We used the Wilcoxon test to assess change in clinical and biological parameters compared to baseline in each group and between the two study groups (delta Δ = difference between values at 60 months and baseline for each patients).

Missing data was handled using the last observation carried forward (LOCF) method. Patients lost to follow-up were excluded from the final analysis for the primary endpoint and we considered them censored data in the survival analyses. P values less than 0.05 (two-sided) were considered statistically significant. Statistical analyses were performed with R studio software V1.1.456.

Results

From March 2001 to October 2009, 49 consecutive French patients were included in the ASTIS study and randomised to the AHSCT ($n = 26$) or the cyclophosphamide ($n = 23$) arms (Fig. 1), of whom 25/26 patients completed the ASHCT procedure and 18/23 patients received all 12 monthly intravenous cyclophosphamide infusions. There was no statistical difference at baseline between the AHSCT and cyclophosphamide treatment groups regarding: age, sex, SSc disease duration, skin, lung, heart and kidney involvement, and HAQ-DI (Table 1). During the 60 months follow-up in the ASTIS-MATHEC cohort: three were lost to follow-up (1 in AHSCT and two in cyclophosphamide group) and ten died: three in the AHSCT group (one during AHSCT procedure, one from disease progression and one from unknown cause) and seven in the cyclophosphamide group (all from disease progression) (Table 2).

A total of 19 events with respiratory, renal, or cardiac event or death occurred during follow-up: 7 events, including 3 deaths in the AHSCT group and 12 events, including 7 deaths in the cyclophosphamide group. There was a trend towards better EFS (73.1% versus 44.9% estimated by KM, $p = 0.06$; hazard ratio 0.42, 95% CI 0.17, 1.07) and OS (88.1% versus 68.0% estimated by KM, $p = 0.08$; hazard ratio = 0.32 (95% CI: 0.08–1.24), in the AHSCT compared to the cyclophosphamide groups, although this did not reach statistical significance (Fig. 2).

In ITT analysis, AHSCT was superior to cyclophosphamide at 60 months when measured using the GRCS (median: 9 versus −19, $p = 0.02$ (Fig. 3). Among the 525 pairwise comparisons, 64% favoured AHSCT, while 29%

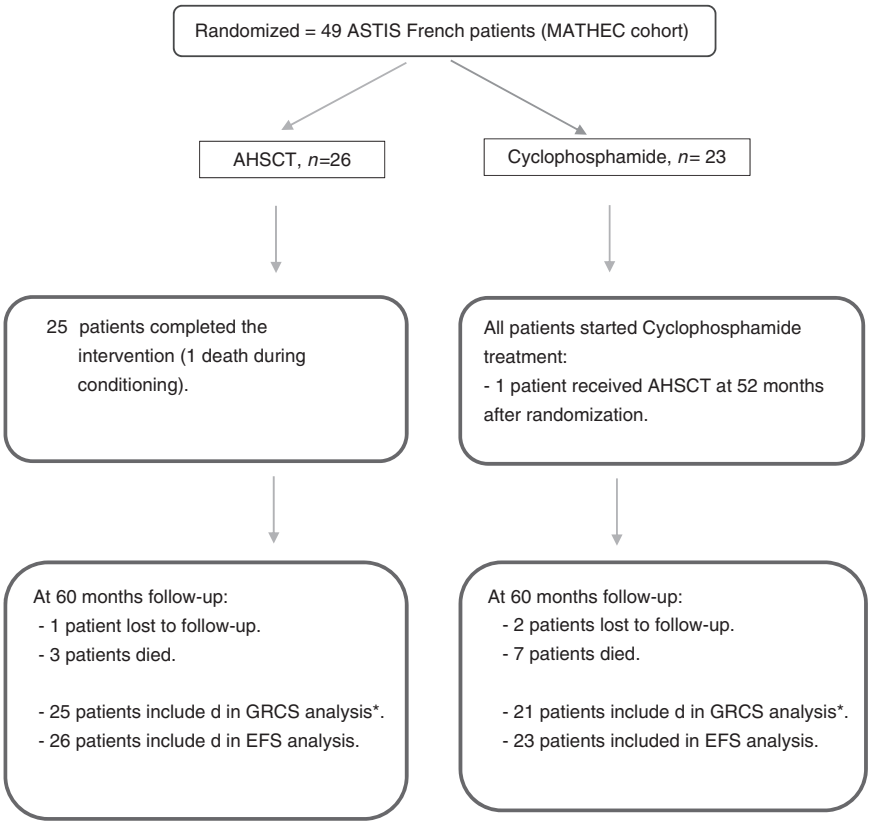

Fig. 1 Flow diagram. AHSCT Autologous Hematopoietic Stem Cell Transplantation, EFS event-free survival, GRCS global rank composite score. *GRCS analysis excluded patients lost to follow up.

favoured cyclophosphamide, $p = 0.02$). Both AHSCT and cyclophosphamide patients showed significant improvement in mRSS at 60 months compared to baseline (25.08 versus 9.18, $p < 0.001$ in AHSCT and 25.52 versus 15.71, $p = 0.01$ in cyclophosphamide), which was significantly greater in the AHSCT compared to cyclophosphamide group (Δ mRSS: −16 versus −9, $p = 0.02$). As compared to baseline, HAQ-DI scores at 60 months improved significantly after AHSCT (1.2 versus 0.41, $P < 0.001$), but not after iv cyclophosphamide (1.3 versus 1.04, $p = 0.25$). The difference in HAQ-DI scores in the AHSCT compared to the cyclophosphamide group favoured AHSCT and this approached statistical significance (Δ HAQ-DI −0.89 versus −0.2, $p = 0.05$). When comparing AHSCT to cyclophosphamide at 60 months, there was no statistically significant differences in FVC (Δ FVC = + 7.36% versus −0.86%, $p = 0.12$), DLCO (Δ DLCO: −2.62% versus −3.29%, $p = 0.99$), heart (Δ LVEF = −0.59% versus −5.7 %, $p = 0.18$) and renal function (Δ serum creatinine = 4.96 µmol/l versus −1.57 µmol/l, $p = 0.21$) in the two treatment groups at 60 months as compared to baseline (Fig. 4).

Discussion

The extended ASTIS-MATHEC cohort study of SSc French patients showed the superiority of non-myeloablative AHSCT compared with Cyclophosphamide at 60 months follow-up using the SCOT-GRCS as primary endpoint to assess combined mortality and morbidity. This was associated with a greater mRSS and HAQ-DI improvement, allowing to expand previous ASTIS findings on a relatively small number of 49 patients. Such results, all obtained in ITT, first allowed to homogenise the assessment criteria from the two large ASTIS [11] and SCOT [12] trials and also improve our understanding of the respective benefits from myeloblative and non-myelaoablative conditioning regimen during AHSCT for severe SSc.

Choosing the best endpoint to assess AHSCT efficacy is a challenge in SSc [16, 17] since endpoints of interest require prior validation, especially for relapse or progression. Indeed, uniform definition of remission or cure is missing for SSc, an orphan disease with few long term outcome data. Several parameters, previously established as strong predictors of survival, such as the mRSS [18] or the FVC [19], are classicaly used to assess SSc therapies. However, these single measures do not consider the multi-organ involvement nor the heterogeneity of the numerous parameters contributing to disease progression. Recently, the ACR developed the Composite Response Index for SSc [20], which integrates change in mRSS, FVC, HAQ-DI, physician and patient global assessments (PGA) of scleroderma-related health to assess clinical response in SSc trials. However, PGA was not

Table 1 Baseline characteristics of 49 French patients with severe Systemic Sclerosis initially treated in the ASTIS randomised controlled trial with Autologous Hematopoietic Stem Cell Transplantation (AHSCT) ($n = 26$ patients) or 12 monthly iv infusions of cyclophosphamide ($n = 23$ patients).

	Total	AHSCT	Cyclophosphamide	*p*
Age	44.11 (12.34)	46.06 (12.70)	41.90 (11.80)	0.17
Gender				0.77
Women	30 (61.22%)	15 (57.69%)	15 (65.22%)	
Men	19 (38.78%)	11 (42.31%)	8 (34.78% = 17)	
Geographic origin				0.78
Caucasian	32 (65.31%)	19 (73.08%)	13 (56.52%)	
North African	7 (14.29%)	3 (11.54%)	4 (17.39%)	
Asian	2 (4.08%)	1 (3.85%)	1 (4.35%)	
Middle Eastern	1 (2.04%)	0 (0%)	1 (4.35%)	
Other	7 (14.29%)	3 (11.54%)	4 (17.39%)	
Smoking status				0.58
Current	32 (65.31%)	19 (73.08%)	13 (56.52%)	
Former	10 (20.41%)	4 (15.38%)	6 (26.09%)	
Never	7 (14.29%)	3 (11.54%)	4 (17.39%)	
Time since SSc diagnosis (year)	1.51 (1.15)	1.56 (1.23)	1.44 (1.08)	0.82
Previous use of Cyc	8 (16.33%)	3 (11.54%)	5 (22.73%)	0.44
Dose delivered of Cyc (g)	1.7 (1.2)	2.1 (1.9)	1.6 (1.2)	0.85
Major organ involvement				
Lung	41 (83.67%)	20 (76.29%)	21 (91.30%)	0.25
Cardiac	4 (8.16%)	2 (7.69%)	2 (8.70%)	1
Renal	0	0	0	1
BMI (Kg/m²)	22.73 (3.68)	23.80 (3.97)	21.52 (3.42)	0.06
mRSS	25.29 (8.24)	25.08 (7.56)	25.52 (9.11)	0.90
Pulmonary				
Forced vital capacity, %	81.69 (19.91)	83.03 (22.66)	80.17 (16.65)	0.59
Total lung capacity, %	82.84 (18.56)	85.59 (17.59)	79.74 (19.51)	0.23
DLCO, %	57.89 (15.08)	61.62 (16.51)	53.49 (12.11)	0.06
Abnormal thoracic HRCT	42 (85.71%)	24 (92.30%)	18 (78.26%)	0.23
Cardiac				
Abnormal ECG	40 (81.63%)	21 (84%)	19 (82.61%)	1
LVEF (%)	66.79 (7.78)	65.50 (8.54)	68.38 (6.58)	0.21
PAH	9 (18.37%)	3 (12.50%)	6 (27.27%)	0.28
SPAP	30.3 (7.38)	29.22 (7.81)	31.43 (6.92)	0.21
Creatinine (µmol/l)	63.89 (13.2)	66.44 (11.82)	60.16 (14.38)	0.11
HAQ-DI	1.23 (0.78)	1.17 (0.72)	1.30 (0.85)	0.68
Disease duration <2 years and mRss >20	6 (12.24%)	4 (15.38%)	2 (8.7%)	0.67
Positive ANA status	45 (91.84%)	24 (92.31%)	21 (91.30%)	1
Positive anti SCL70 status	32 (65.31%)	15 (60%)	17 (73.91%)	0.37
Positive ACA status	2 (4.08%)	2 (7.69%)	0 (0%)	0.74

Continuous variables are reported in Mean and standard deviation [Mean (SD)] and categorical variables in number and percent [*N* (%)].

Definitions:

BMI: calculated as weight in kilograms divided by height in metres squared.

Abnormal thoracic HRCT: interstitial lung disease on HR-CT scan related to scleroderma.

Abnormal ECG: defined as the presence of atrial or ventricular rhythm disturbances (recurrent episodes of atrial fibrillation or flutter, recurrent atrial paroxysmal tachycardia or ventricular tachycardia), second- or third-degree AV block, or diffuse micro-voltage or repolarization abnormalities related to pericardial effusion, no-related to scleroderma causes were excluded.

PAH: defined as a mean pulmonary artery pressure greater than 25 mmHg and less than 50 mmHg, measured by cardiac echocardiography or catheterisation of the right side of the heart.

TRT treatment, *Cyc* cyclophosphamide, *BMI* body mass index, *mRss* modified Rodnan skin score, *DLCO* lung diffusion capacity for carbon monoxide, *HRCT* high resolution computed tomography, *ECG* electrocardiogram, *LVEF* left ventricular ejection fraction on echocardiography, *PAH* pulmonary arterial hypertension, *SPAP* systolic pulmonary artery pressure, *HAQ-DI* the Health Assessment Questionnaire Disability Index, *ANA* antinuclear antibody, *AntiSCL70* anti-topoisomerase, *ACA* anticentromere.

Table 2 Death during the 60 months of follow-up.

Group and time from randomisation to death	Cause of death	Completed treatment
Cyclophosphamide group		
18.4 month	Respiratory failure.	Yes
40.8 month	Respiratory failure, cachexia.	Yes
15.8 month	Septic shock, respiratory failure.	No (six doses of cyclophosphamide)
51.9 month	Multi-organ failure due to disease progression.	Yes
4.3 month	Cardiac and respiratory failure.	No (four doses of cyclophosphamide)
46.4 month	Arrhythmia and heart involvement.	Yes
22.7 month	Respiratory failure, cachexia.	No (six doses of cyclophosphamide)
AHSCT group		
55.4 month	Heart involvement, lung fibrosis.	Yes
49.7 month	Unknown cause.	Yes
3.5 month	Sepsis and massive ischaemic stroke.	No (death during conditioning)

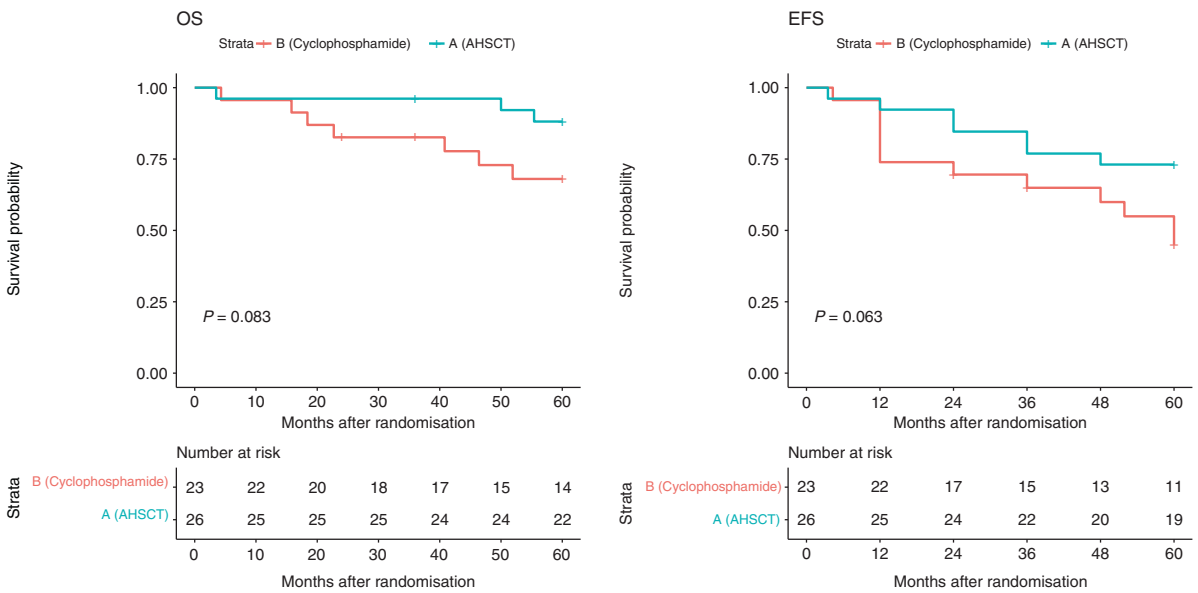

Fig. 2 Overall Survival (OS) and Event-Free Survival (EFS) during 60-Months follow-up. All 49 French ASTIS patients were subsequently included in the prospective Maladies Auto-Immunes et Therapie Cellulaire (MATHEC) cohort for extended follow-up after randomisation for Autologous Hematopoietic Stem Cell Transplantation (AHSCT) (A, blue line, $n = 26$ patients) or 12 monthly iv infusions of cyclophosphamide (B, red line, $n = 23$ patients). Time is in months after randomisation.

collected in ASTIS nor in SCOT patients and this score, which is still being validated in ongoing prospective trials [21], does not capture the impact of mortality.

Concept familiar to HSCT practice, such as the definition for OS and progression-free survival (PFS), were unusual for rheumatologists, when designing early AHSCT studies in SSc. Both ASTIS and SCOT were initially designed using the EFS as primary endpoint, defined as time from randomisation until death from any cause or persistent major heart, lung, or kidney failure [11, 12]. In 2014, the ASTIS trial [11] first demonstrated the effectiveness of non-myeloablative AHSCT on morbidity and mortality up to 10 years in severe SSc based on EFS, a classical primary judgement criteria in haematology. Specific organ damage and functional status were evaluated as secondary endpoints at 2 years. In 2018, the SCOT trial [12] demonstrated the efficacy of myeloablative AHSCT in SSc, using the GRCS as primary endpoint, which combined in a single approach the evaluation of morbidity and mortality and the evolution of SSc-

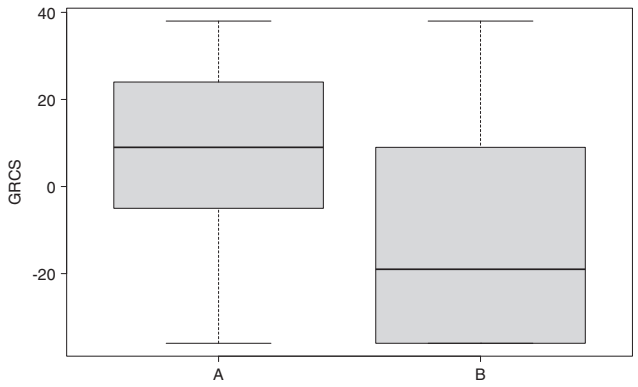

Fig. 3 Distribution of GRCS at 60-months follow-up of the 46 French patients with severe Systemic Sclerosis after randomisation in the ASTIS trial and further extended follow-up. Autologous Hematopoietic Stem Cell Transplantation (A, $n = 25$ patients), 12 monthly iv infusions of cyclophosphamide (B, $n = 21$ patients).

retained great attention and it was the first time that the GRCS, a powerful non-parametric statistical tool, was used to analyse the effect of treatment in rheumatology.

The GRCS is a statistical method, which combines an event with a longitudinal measure of clinical effect, was first developed and validated by Finkelstein and Schoenfeld [22] in therapeutic trials for paediatric HIV. Its principle is based on comparing each patient in the clinical trial to every other patient in a pairwise manner. Patients are initially compared on survival and otherwise compared on the other endpoints, in a hierarchical order based on the relative severity of the possible outcomes. The GRCS combined the measures with the same clinical meaning, including mortality as the first element of comparison, allowing to increase the power of a study without introducing the risk of misleading [22]. In SCOT trial [12], the GRCS allowed to show the superiority of myeloablative AHSCT, while the superiority of EFS in

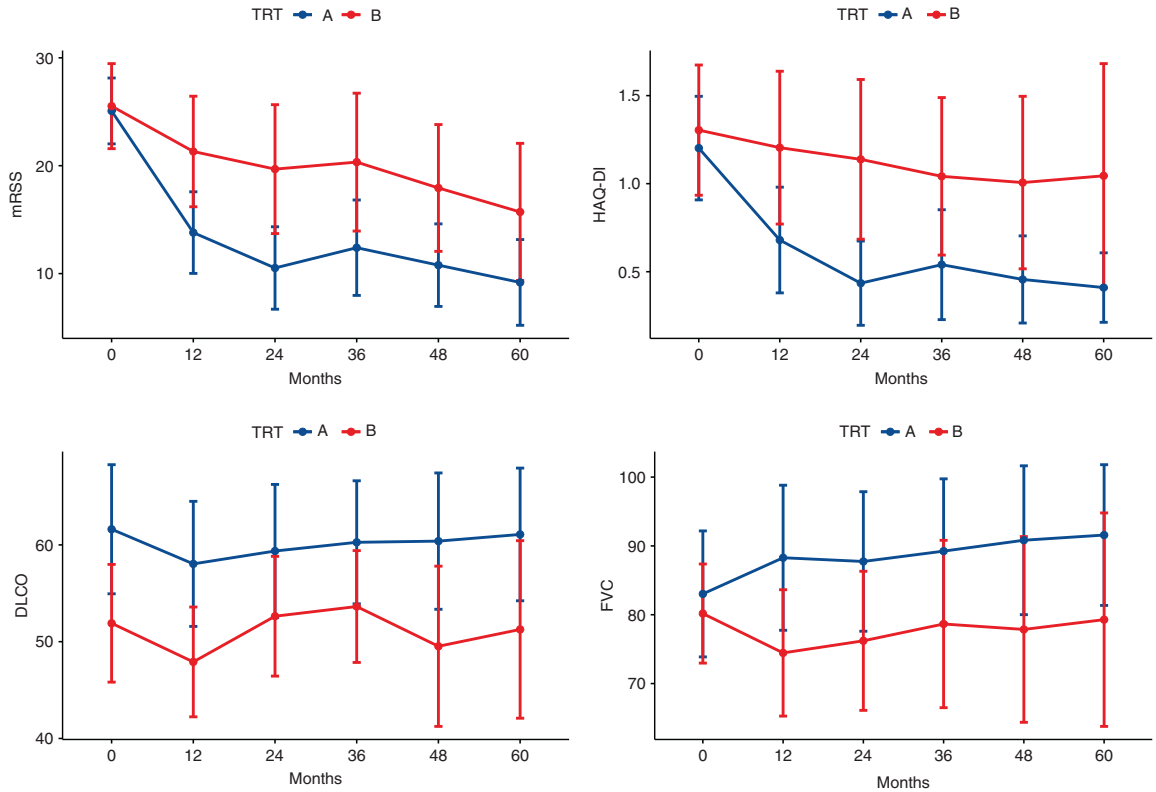

Fig. 4 Change in modified Rodnan skin score (mRss), Health Assessment Questionnaire Disability Index (HAQ-DI), forced vital capacity (FVC) and lung diffusion capacity for carbon monoxide (DLCO) during the 60 months of follow-up. The 49 French patients with severe Systemic Sclerosis were initially treated in the ASTIS randomised controlled trial with Autologous Hematopoietic Stem Cell Transplantation (AHSCT) (A, blue line, $n = 26$ patients) or 12 monthly iv infusions of cyclophosphamide (B red line, $n = 23$ patients) and underwent further extended follow-up.

specific outcomes. This was obtained after modifying the SCOT protocol, initially designed as a phase 3 study with EFS analysis at 44 months of follow-up and a sample size of 226 patients, to a phase 2 study using GRCS at 54 months with 75 randomised patients. SCOT results the AHSCT group was only found in the per-protocol analysis. In the ASTIS-MATHEC study, the GRCS showed the superiority of non-myelobablative AHSCT with a difference between the two study groups at long term, despite a small number of patients. Therefore, using the GRCS tool

allowed to reconcile the results from ASTIS and SCOT trials and to further demonstrate the efficacy of non-myeloablative AHSCT and myelobablative AHSCT in severe SSC patients. In addition, when using a single judgement criteria, namely the mRSS or the HAQ-DI at 60 months follow-up, the superiority of non-myeloabaltive AHSCT versus cyclophosphamide was observed.

Among the 26 French patients transplanted in ASTIS, the transplant related mortality at 100 days was 3.8%, which appeared lower than the 10.1% deemed treatment-related reported among all 79 patients transplanted in ASTIS [11], while no death was reported the first year among the 36 patients transplanted in SCOT trial. These differences may be related to patient selection [23, 24], centre effect [25] or conditioning regimen [26]. In the ASTIS-MATHEC study, the EFS and OS at 60 months were not significantly higher in the non-myeloablative AHSCT group compared to cyclophosphamide, due to relatively low number of patients. Of note, the superiority of EFS and OS in the myeloablative AHSCT group was only shown in per-protocol analysis at 54 months in the SCOT trial, illustrating the complexicity of such trials, which necessitate a significant number of patients to reach significance on classical endpoints such as OS, EFS and PFS in haematology or oncology.

Our study is not without some limitations. Although there was some missing data, this was less than 15% for each study variable. Also, to address this point, we used the LOCF technique, which has the potential to bias results against the intervention. Thus, our results can be viewed as conservative estimates. Also, despite the relatively small number of patients, we obtained statistically significant results in the primary and some secondary outcomes as well as strong trends in several other secondary outcomes while maintaining an ITT analysis.

In conclusion, this study confirms previous knowlegde acquired from SCOT [12] and ASTIS [11] trials and supports the use of the GRCS tool in future SSc trials.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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