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Original Article

Efficacy and safety of autologous hematopoietic stem cell transplantation for refractory systemic sclerosis after rituximab-bendamustine conditioning

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Abstract: Objectives: To evaluate the efficacy and safety of autologous hematopoietic stem cell transplantation (auto-HSCT) using a novel rituximab-bendamustine conditioning regimen in patients with refractory systemic sclerosis (SSc). Methods: This retrospective cohort study enrolled 216 patients with refractory SSc who received treatment between August 2019 and August 2023. Participants were divided into a transplant group (n=104) receiving the novel auto-HSCT regimen, and a conventional group (n=112) treated with prednisone combined with cyclophosphamide. Efficacy indicators, including the modified Rodnan skin score (mRSS), pulmonary, cardiac and renal function, organ involvement manifestations, autoantibody titers, quality of life (SF-36) scores, and clinical remission status, were assessed at baseline and 24 weeks post-treatment. Adverse events and progression-free survival (PFS) were also analyzed. Results: At the 24-week follow-up, the transplant group achieved significantly greater mRSS improvement (P<0.001). Significant improvements were also observed in pulmonary function (forced vital capacity [FVC], P=0.009) and cardiac function (left ventricular ejection fraction [LVEF], P=0.005) in the transplant group. The transplant group had a higher overall clinical remission rate (75.00% vs. 60.71%) and longer PFS (all P<0.05). Infusion reactions were more prevalent in the transplant group (15.38% vs. 4.46%), whereas gastrointestinal reactions and hyperglycemia occurred more frequently in the conventional group. Conclusion: Auto-HSCT with a rituximab-bendamustine conditioning regimen yields superior improvements in multi-organ lesions and long-term survival outcomes in patients with refractory SSc compared with conventional therapy, with a tolerable safety profile.

Keywords: Systemic sclerosis, autologous hematopoietic stem cell transplantation, rituximab, bendamustine, refractory disease

Introduction

Systemic sclerosis (SSc) is a complex, disabling autoimmune disease characterized by widespread vasculopathy, immune dysregulation, and progressive fibrosis of the skin and internal organs [1, 2]. Its clinical course is highly heterogeneous, yet a substantial proportion of patients develop rapidly progressive diffuse cutaneous SSc, which often causes severe disability and high mortality due to progressive involvement of vital organs including the lungs, heart, and kidneys [3, 4].

Conventional immunosuppressive therapies are often insufficient for patients with aggressive, refractory SSc. Cyclophosphamide- or mycophenolate mofetil-based regimens serve as the first-line standard treatment, yet a large number of patients only achieve partial or transient treatment responses. These patients experience continuous disease progression, eventually developing irreversible organ damage and reduced life expectancy. This unmet clinical need necessitates the development of more potent therapeutic strategies to alter the natural course of SSc [5, 6].

Autologous hematopoietic stem cell transplantation (AHSCT) has emerged as a curative-intent intervention for severe autoimmune diseases. This procedure aims to ablate the dysfunctional immune system and reconstruct a tolerant, functional immune system via reinfu-

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sion of autologous stem cells [7]. In SSc, clinical trials have demonstrated that AHSCT can induce profound, sustained improvements in skin thickening, stabilize and restore lung function, and provide significant survival benefits over conventional cyclophosphamide therapy. These therapeutic advantages are attributed to the potent immunosuppressive effects of high-dose conditioning regimens administered prior to stem cell reinfusion [8, 9].

Accordingly, the formulation of conditioning regimens is critical to treatment efficacy. Traditional conditioning regimens for SSc, such as single-agent cyclophosphamide or cyclophosphamide combined with anti-thymocyte globulin, can reset immune function but are associated with substantial toxicity and high relapse rates, highlighting the urgent need for more targeted and efficient conditioning protocols [10, 11]. Rituximab is a monoclonal antibody targeting CD20 on B cells, which are key mediators of autoimmunity and fibrosis in SSc [12]. Bendamustine is a unique alkylating agent with proven efficacy in B-cell malignancies and certain autoimmune diseases, exerting potent cytotoxic effects while maintaining a favorable safety profile for stem cell mobilization and conditioning [13].

The synergistic effects of rituximab combined with bendamustine in AHSCT constitute a novel therapeutic hypothesis for refractory SSc. This combination may enhance the depletion of B cells and plasma cells, thereby more effectively eliminating pathogenic immune memory and potentially reducing regimen-related toxicity. Currently, high-quality clinical data on the efficacy and safety of rituximab-bendamustine-based conditioning regimens for AHSCT in refractory SSc remain scarce. Therefore, this study aimed to evaluate the clinical outcomes and safety profile of AHSCT with a novel rituximab-bendamustine-containing conditioning regimen in patients with refractory systemic sclerosis.

Materials and methods

Research ethics

This retrospective study was conducted in accordance with the principles of the Declaration of Helsinki and approved by the Institutional Review Board (IRB) of Pu'er People's Hospital. Informed consent was waived due to the use of anonymized medical records. All patient data were de-identified to ensure complete privacy protection.

Screening criteria

Inclusion criteria: Patients aged 18 to 70 years; diagnosed with SSc in accordance with the 1980 American College of Rheumatology (ACR) classification criteria [14], with a disease duration of no less than 6 months; refractory to conventional immunosuppressive therapy (defined as receiving at least one course of cyclophosphamide or mycophenolate mofetil treatment, with less than 30% mRSS improvement after 6 months of standardized treatment or progressive visceral organ involvement); baseline mRSS ≥25; positive for at least one autoantibody (antinuclear antibody [ANA] titer ≥1:1000 via immunofluorescence assay and/or positive anti-Scl-70 antibody); and with complete clinical data and 2-year follow-up records.

Exclusion criteria: Pregnant or breastfeeding women; patients with scleroderma renal crisis (SRC) within 30 days prior to enrollment, defined as acute kidney injury, rapidly elevated blood pressure, and progressive increase in serum creatinine secondary to SSc; patients with active, uncontrolled infections requiring intravenous antimicrobial therapy or ongoing treatment for chronic infection; patients with active tuberculosis confirmed by chest imaging within 6 months before enrollment; and patients with severe uncontrolled comorbidities deemed unsuitable for high-intensity immunosuppressive therapy or hematopoietic stem cell transplantation by the investigators.

Study design and grouping

This retrospective cohort study enrolled 216 patients with refractory systemic sclerosis who failed to respond to conventional immunosuppressive therapy and received treatment at Pu'er People's Hospital from August 2019 to August 2023. All data were extracted from the hospital's electronic medical record system. Patients were stratified into two groups based on their treatment regimens: the transplant group (n=104) received auto-HSCT with rituximab-bendamustine conditioning, and the conventional group (n=112) received standard immunosuppressive therapy consisting of prednisone plus cyclophosphamide pulse therapy.

Statistical methods

SPSS 24.0 software (IBM, USA) was used for all statistical analyses. The Shapiro-Wilk test was applied to assess data normality. Continuous variables conforming to normal distribution were expressed as mean ± standard deviation (SD), and intergroup differences were compared using independent samples t-tests. Categorical variables were presented as frequencies and percentages, with between-group comparisons performed via the chi-square test. Kaplan-Meier curves were plotted to analyze PFS, and the log-rank test was used for intergroup comparison. Given the retrospective study design, multivariate linear regression analysis was further performed for the primary endpoint (24-week mRSS), with all baseline characteristics included as covariates. The results were reported as regression coefficients (β) with 95% confidence intervals (CIs). All statistical tests were two-tailed, and a *P* value <0.05 was considered statistically significant. No data were missing for any outcome indicator in this study.

Treatment protocols

Transplant group: Mobilization, Collection, Purification, and Cryopreservation of Autologous Peripheral Blood Stem Cells: The stem cell mobilization regimen consisted of 3 g/m^2 cyclophosphamide (CTX, Shanxi Pude Pharmaceutical Co., Ltd., H14023686) administered intravenously over two consecutive days. When peripheral blood leukocyte counts reached the nadir and began to recover, subcutaneous injection of recombinant human granulocyte colony-stimulating factor (G-CSF, Harbin Pharmaceutical Group Bioengineering Co., Ltd., S20000061) at a daily dose of 10 μg/kg was initiated. Peripheral blood stem cells were collected using a COM.TEC blood cell separator (Fresenius Kabi, Germany) when peripheral mononuclear cell counts exceeded 5 × 10^9/L. The circulating blood volume for collection was 2 to 3 times the patient's total blood volume, with a target CD34+ cell counts >2 × 10^6/kg; one to two collection sessions were required for most patients. Collected stem cell products were cryopreserved at -80°C using dimethyl sulfoxide as a cryoprotectant.

Conditioning Regimen: Rituximab (RTX, Shanghai Henlius Biopharmaceuticals Co., Ltd., S20190021) 375 mg/m^2 was administered intravenously on day 1; bendamustine (Ben, CTD Pharma Co., Ltd., H20193358) 90 mg/m^2 was administered intravenously on days 2 and 3; CTX 50 mg/kg/day was administered intravenously from day 2 to day 5.

Supportive Therapy and Complication Prevention: One week before admission to the laminar airflow clean ward, patients received oral intestinal decontamination medications, including fluconazole (Guangdong Yishu Pharmaceutical Co., Ltd., H20066085), compound sulfamethoxazole (Shanghai XinYa Pharmaceutical Minhang Co., Ltd., H31020387), and norfloxacin (CSPC Ouyi Pharmaceutical Co., Ltd., H13022807). All patients received a whole-body bath with 1:2000 diluted chlorhexidine acetate and underwent subclavian venous catheterization prior to ward admission. Mesna (Jiangsu Hengrui Medicine Co., Ltd., H10950290) was infused intravenously during and after high-dose CTX administration for bladder protection. Red blood cell transfusion was performed when hemoglobin levels dropped below 60 g/L or patients presented with severe anemia symptoms. Platelet transfusion was administered when platelet counts decreased below 20 × 10^9/L or active bleeding occurred. Starting from day 2 after stem cell reinfusion, subcutaneous G-CSF injection was administered to promote hematopoietic recovery until neutrophil counts stabilized and increased sustainably.

Conventional group: Patients received oral prednisone tablets (Chenxin Pharmaceutical Co., Ltd., H37021900) at an initial daily dose of 1 mg/kg. After 4 weeks of treatment, the prednisone dose was gradually reduced by 10% of the initial dose weekly, with individualized adjustments to the minimum maintenance dose or discontinuation based on patient condition. Meanwhile, all patients received intravenous CTX pulse therapy consistent with the conventional clinical protocol: 0.5 g per session, once every 2 weeks, for a total of 12 sessions over the 24-week treatment period.

Evaluation indicators and methods

Skin thickness assessment: Skin thickness was assessed using the modified Rodnan skin score (mRSS) [15]. Two rheumatologists blinded to group allocation independently palpated

and scored 17 body regions (face, chest, abdomen, upper arms, forearms, dorsal hands, fingers, thighs, lower legs, and dorsal feet). Each region was scored on a 0-3 scale (0 = normal, 1 = mild thickening, 2 = moderate thickening, 3 = severe thickening), with a total score ranging from 0 to 51. The final mRSS for each patient was the average of the two physicians' scores.

Pulmonary function assessment: Pulmonary Ventilation Function: Forced vital capacity (FVC) was measured using a MasterScreen PFT spirometer (CareFusion, Germany). A professional technician guided patients to complete standardized testing, and the mean value of the three optimal measurements was recorded in liters (L).

Pulmonary Diffusion Function: The diffusing capacity for carbon monoxide (DLCO) was measured using the carbon monoxide diffusion module of the same spirometer, with results expressed as a percentage of the predicted normal value (%).

High-Resolution CT (HRCT) Scoring: HRCT scanning was performed using a SOMATOM Definition Flash scanner (Siemens, Germany). Two radiologists blinded to group allocation evaluated lung lesions using the semi-quantitative Warrick scoring system. The severity of ground-glass opacity and fibrosis in the upper, middle, and lower zones of both lungs was each scored 0-3, with a total cumulative score ranging from 0 to 36. The final HRCT score was the average of the two radiologists' independent scores.

Cardiac function assessment: Cardiac function was assessed via Vivid E95 echocardiography (GE Healthcare, USA). The biplane Simpson method was used to measure left ventricular ejection fraction (LVEF). Pulmonary artery systolic pressure (PASP) was calculated using the simplified Bernoulli equation based on the peak tricuspid regurgitation velocity.

Renal function assessment: Fasting venous blood samples were collected to detect serum creatinine (SCr) and blood urea nitrogen (BUN) levels using a fully automatic biochemical analyzer (Cobas c 702, Roche, Switzerland). The estimated glomerular filtration rate (eGFR) was calculated via the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation based on SCr levels. Patients were instructed to collect 24-hour urine samples completely and accurately. After thorough mixing, total urine volume was recorded, and urine samples were tested for protein concentration to calculate 24-hour urinary protein excretion (g/24 h).

Organ-specific manifestation assessment: Organ-specific manifestations were systematically recorded via standardized medical history collection and physical examination. Raynaud's phenomenon was defined as typical triphasic color changes (pallor-cyanosis-erythema) of the fingers or toes induced by cold stimulation or emotional stress. Digital ulcers were defined as visible skin defects or necrotic scabs at the fingertip or toe tip.

Autoantibody titer assessment: Venous blood samples were collected and centrifuged to separate serum for antibody detection. ANA titers were measured via indirect immunofluorescence assay on HEp-2 cell substrates (EUROPattern, EUROIMMUN, Germany). Anti-Scl-70 antibody levels were detected by immunoblot assay (Euroline, EUROIMMUN, Germany) and reported as quantitative or semi-quantitative values.

Health-related quality of life assessment: The Chinese version of the 36-Item Short Form Health Survey (SF-36) was used to evaluate patients' health-related quality of life [16]. The scale covers eight dimensions: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health. Each dimension is standardized to a score of 0-100, with higher scores indicating better health status.

Clinical remission assessment: A comprehensive clinical efficacy evaluation was performed at 24 weeks post-treatment. Clinical remission was classified into three grades: Complete Remission (CR) was defined as >80% mRSS improvement from baseline without new or progressive visceral organ involvement; Partial Remission (PR) was defined as 30%-80% mRSS improvement from baseline without new or progressive visceral organ involvement; No Remission (NR) was defined as <30% mRSS improvement from baseline or the presence of new/progressive visceral organ lesions. The overall remission rate (ORR) was calculated as the sum of CR and PR rates.

Table 1. General information of the subjects

Parameters	Conventional group (n=112)	Transplant group (n=104)	t/χ^2	P
Age (years)	48.52 ± 6.31	47.89 ± 6.15	0.733	0.464
Gender (male/female)	40 (35.71%)	38 (36.54%)	0.016	0.900
BMI (kg/m^2)	22.45 ± 2.05	22.67 ± 2.11	0.770	0.442
Living condition (urban/rural) (n, %)	78 (69.64%)	74 (71.15%)	0.059	0.808
Education level (high school and below/university and above) (n, %)	65 (58.04%)	58 (55.77%)	0.113	0.737
Employment (n, %)	52 (46.43%)	50 (48.08%)	0.059	0.808
Smoking history (n, %)	23 (20.54%)	20 (19.23%)	0.058	0.810
Drinking history (n, %)	18 (16.07%)	15 (14.42%)	0.113	0.737
Duration of illness (months)	24.58 ± 8.17	25.80 ± 8.20	1.096	0.274
Autoantibody subtype (n, %)				
Anti-Scl-70 positive	71 (63.39%)	68 (65.38%)	0.093	0.760
ACA positive	15 (13.39%)	12 (11.54%)	0.170	0.681
Comorbidity (n, %)				
Hypertension	32 (28.57%)	28 (26.92%)	0.073	0.787
Diabetes Mellitus	19 (16.96%)	16 (15.38%)	0.099	0.753
Interstitial Lung Disease	70 (62.5%)	68 (65.4%)	0.194	0.659

BMI, Body Mass Index; ACA, Anticentromere Antibody.

Safety assessment: All adverse events occurring from treatment initiation to the final follow-up were recorded and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 [17]. Focused safety indicators included infection, liver injury (alanine aminotransferase/aspartate aminotransferase elevation >3 times the upper limit of normal), kidney injury (SCr elevation ≥1.5 times the baseline level), cardiovascular events, drug infusion reactions, gastrointestinal reactions, and hyperglycemia.

Progression-free survival assessment: PFS was defined as the interval from treatment initiation to the first occurrence of disease progression or all-cause death. Disease progression was defined as a >25% increase in mRSS relative to the lowest post-treatment value and/or the emergence or definite progression of visceral (lung, heart, kidney) lesions confirmed by imaging or functional tests. Patients without endpoint events were censored at the last follow-up date.

Data collection

Two trained researchers independently extracted all data from the electronic medical record system using standardized data collection forms. Collected data included baseline clinical characteristics, treatment regimens, efficacy indicators, and adverse events. All efficacy evaluations were performed at baseline and 24 weeks after treatment initiation.

Results

Comparison of baseline clinical characteristics

All enrolled patients had diffuse cutaneous SSc with baseline mRSS ≥25, consistent with the inclusion criteria. There were no significant intergroup differences in age, gender distribution, body mass index (BMI), living condition, educational level, employment status, smoking history, drinking history, disease duration, positive anti-Scl-70 antibody rate, positive anticentromere antibody rate, or comorbidities including hypertension, diabetes mellitus and interstitial lung disease (all P>0.05). Baseline characteristics were well balanced between the two groups, ensuring good intergroup comparability (**Table 1**).

Comparison of modified Rodnan skin score

Baseline mRSS was comparable between the two groups (P=0.738). At 4 weeks post-treatment, the transplant group showed a significantly lower mRSS than the conventional group (18.23 ± 4.12 vs. 24.56 ± 5.01, t=10.175, P<0.001). This significant difference persisted at 12 weeks (12.45 ± 3.56 vs. 20.14 ± 4.78,

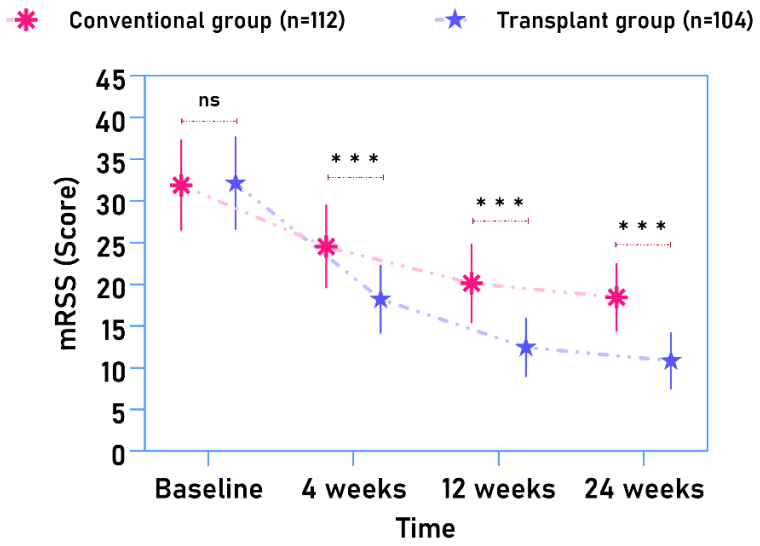

Figure 1. Changes in mRSS of the subjects before and after treatment. mRSS, Modified Rodnan Skin Score. Data are presented as mean ± SD. The comparison between groups was performed using an independent samples t-test. ns, no statistically significant difference; ***, P<0.001.

Table 2. Pulmonary function and HRCT scores of the subjects before and after treatment

Parameters		Conventional group (n=112)	Transplant group (n=104)	t	P
FVC (L)	Baseline	2.48 ± 0.58	2.45 ± 0.56	0.303	0.762
	24 weeks	2.60 ± 0.59	2.82 ± 0.63	2.653	0.009
DLCO (%)	Baseline	57.89 ± 10.45	60.12 ± 10.78	1.543	0.124
	24 weeks	58.34 ± 10.23	63.10 ± 12.21	3.113	0.002
HRCT Score	Baseline	18.53 ± 4.26	18.95 ± 4.01	0.749	0.455
	24 weeks	16.22 ± 3.94	14.56 ± 3.62	3.219	0.001

FVC, Forced Vital Capacity; DLCO, Diffusing Capacity of the Lung for Carbon Monoxide; HRCT, High-Resolution Computed Tomography (a semi-quantitative score).

Table 3. Cardiac function parameters of the subjects before and after treatment

Parameters		Conventional group (n=112)	Transplant group (n=104)	t	P
LVEF (%)	Baseline	58.12 ± 6.45	58.45 ± 6.23	0.378	0.706
	24 weeks	59.23 ± 6.12	61.54 ± 5.89	2.823	0.005
PASP (mmHg)	Baseline	43.12 ± 8.45	42.34 ± 8.12	0.693	0.489
	24 weeks	41.56 ± 8.12	38.35 ± 7.23	3.055	0.003

LVEF, Left Ventricular Ejection Fraction; PASP, Pulmonary Artery Systolic Pressure.

t=13.492, P<0.001) and 24 weeks (10.85 ± 3.41 vs. 18.45 ± 4.12, t=14.723, P<0.001). These findings indicated that the transplant group achieved significantly greater and faster mRSS reduction throughout the treatment period (**Figure 1**).

Comparison of pulmonary function and imaging outcomes

Baseline FVC, DLCO and HRCT scores were similar between the two groups (all P>0.05). At 24 weeks post-treatment, the transplant group exhibited significantly superior improvements in FVC (2.82 ± 0.63 L vs. 2.60 ± 0.59 L, t=2.653, P=0.009), DLCO (63.10 ± 12.21% vs. 58.34 ± 10.23%, t=3.113, P=0.002), and HRCT scores (14.56 ± 3.62 vs. 16.22 ± 3.94, t=3.219, P=0.001) compared with the conventional group, demonstrating better pulmonary functional recovery and reduced lung lesion severity in the transplant group (**Table 2**).

Comparison of cardiac function parameters

Baseline LVEF and PASP levels were comparable between the two groups (all P>0.05). At 24 weeks post-treatment, the transplant group had significantly higher LVEF (61.54 ± 5.89% vs. 59.23 ± 6.12%, t=2.823, P=0.005) and lower PASP (38.35 ± 7.23 mmHg vs. 41.56 ± 8.12 mmHg, t=3.055, P=0.003), indicating superior cardiac functional preservation and improvement in the transplant group (**Table 3**).

Comparison of renal function indicators

Baseline SCr, BUN, eGFR and 24-hour urinary protein levels showed no significant intergroup differences (all P>0.05). At 24 weeks post-treatment, the transplant group had a significantly higher eGFR (93.15 ± 10.88 ml/min/1.73 m^2 vs. 89.84 ± 10.37 ml/min/1.73 m^2, t=2.293, P=0.023) and lower 24-hour urinary protein excretion (2.25 ± 0.71 g/24 h vs. 3.13 ± 0.82 g/24 h, t=8.386,

Table 4. Renal function indicators before and after treatment

Parameters		Conventional group (n=112)	Transplant group (n=104)	t	P
Scr (μmol/L)	Baseline	89.72 ± 15.13	88.24 ± 15.17	0.715	0.476
	24 weeks	83.31 ± 14.14	80.29 ± 13.56	1.597	0.112
BUN (mmol/L)	Baseline	6.91 ± 1.23	7.01 ± 1.32	0.532	0.595
	24 weeks	6.12 ± 1.17	5.87 ± 1.11	1.634	0.104
eGFR (ml/min/1.73 m^2)	Baseline	84.63 ± 10.24	86.34 ± 10.37	1.217	0.225
	24 weeks	89.84 ± 10.37	93.15 ± 10.88	2.293	0.023
24-h Urine Protein (g/24 h)	Baseline	6.49 ± 1.52	6.54 ± 1.62	0.250	0.803
	24 weeks	3.13 ± 0.82	2.25 ± 0.71	8.386	<0.001

Scr, Serum Creatinine; BUN, Blood Urea Nitrogen; eGFR, Estimated Glomerular Filtration Rate.

Table 5. Organ-specific manifestations before and after treatment

Parameters		Conventional group (n=112)	Transplant group (n=104)	χ^2	P
Raynaud's Phenomenon (n, %)	Baseline	105 (93.75%)	98 (94.23%)	0.022	0.882
	24 weeks	98 (87.50%)	75 (72.12%)	8.005	0.005
Digital Ulcers (n, %)	Baseline	67 (59.82%)	62 (59.62%)	0.001	0.975
	24 weeks	58 (51.79%)	38 (36.54%)	5.077	0.024

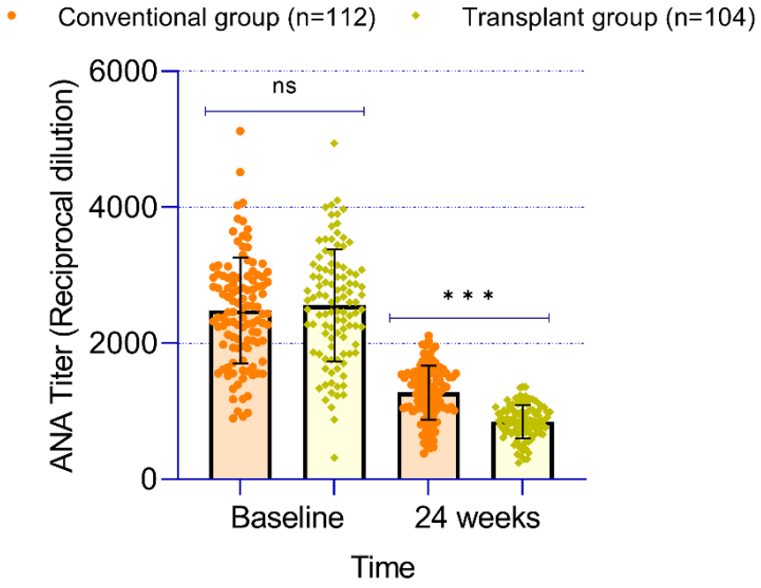

Figure 2. Autoantibody titers of the subjects before and after treatment. ANA, Antinuclear Antibody. Data are presented as mean ± SD. The comparison between groups was performed using an independent samples t-test. ns, no statistically significant difference; ***, P<0.001.

Comparison of organ-specific manifestations

The baseline prevalence of Raynaud's phenomenon and digital ulcers was similar between the two groups (P=0.882, P=0.975, respectively). At 24 weeks post-treatment, the transplant group had a significantly lower prevalence of Raynaud's phenomenon (72.12% vs. 87.50%, χ^2=8.005, P=0.005) and digital ulcers (36.54% vs. 51.79%, χ^2=5.077, P=0.024) than the conventional group, indicating that the novel transplant regimen was more effective in improving SSc-related vascular lesions (**Table 5**).

Comparison of autoantibody titers

P<0.001). No significant intergroup differences were observed in SCr and BUN levels at 24 weeks (all P>0.05). These results confirmed better renal functional improvement in the transplant group (**Table 4**).

Baseline ANA titers were comparable between the two groups (P=0.492). At 24 weeks post-treatment, ANA titers in the transplant group were significantly lower than those in the conventional group (846.92 ± 245.37 vs. 1275.38

Table 6. SF-36 score of the subjects before and after treatment

Parameters		Conventional group (n=112)	Transplant group (n=104)	t	P
Physical Functioning	Baseline	46.12 ± 4.61	45.23 ± 4.52	1.431	0.154
	24 weeks	54.34 ± 5.23	61.20 ± 5.75	9.189	<0.001
Role-Physical	Baseline	42.34 ± 4.23	41.89 ± 4.19	0.786	0.432
	24 weeks	49.56 ± 4.86	54.30 ± 5.50	6.714	<0.001
Bodily Pain	Baseline	44.56 ± 4.46	43.78 ± 4.38	1.307	0.193
	24 weeks	51.23 ± 5.12	58.45 ± 5.90	9.620	<0.001
General Health	Baseline	43.12 ± 4.31	42.34 ± 4.23	1.337	0.183
	24 weeks	51.80 ± 5.15	56.60 ± 5.70	6.493	<0.001
Vitality	Baseline	48.30 ± 4.89	47.56 ± 4.76	1.127	0.261
	24 weeks	55.64 ± 5.41	58.15 ± 6.32	3.137	0.002
Social Functioning	Baseline	49.23 ± 4.92	48.45 ± 4.85	1.174	0.242
	24 weeks	56.78 ± 5.68	58.12 ± 6.25	1.644	0.102
Role-Emotional	Baseline	50.11 ± 5.01	49.67 ± 4.97	0.642	0.522
	24 weeks	57.45 ± 5.75	58.74 ± 6.35	1.569	0.118
Mental Health	Baseline	51.23 ± 5.12	50.12 ± 5.01	1.599	0.111
	24 weeks	59.46 ± 5.98	62.05 ± 6.26	3.118	0.002

± 398.52, t=9.588, P<0.001), suggesting that the rituximab-bendamustine conditioning regimen effectively reduced autoimmune antibody levels (**Figure 2**).

Comparison of health-related quality of life

All SF-36 dimension scores were similar between the two groups at baseline (all P>0.05). At 24 weeks post-treatment, the transplant group achieved significantly higher scores in physical functioning (61.20 ± 5.75 vs. 54.34 ± 5.23, t=9.189, P<0.001), role-physical (54.30 ± 5.50 vs. 49.56 ± 4.86, t=6.714, P<0.001), bodily pain (58.45 ± 5.90 vs. 51.23 ± 5.12, t=9.620, P<0.001), general health (56.60 ± 5.70 vs. 51.80 ± 5.15, t=6.493, P<0.001), vitality (58.15 ± 6.32 vs. 55.64 ± 5.41, t= 3.137, P=0.002), and mental health (62.05 ± 6.26 vs. 59.46 ± 5.98, t=3.118, P=0.002). No significant intergroup differences were found in social functioning and role-emotional scores (all P>0.05) (**Table 6**).

Comparison of clinical remission rate

Significant intergroup differences in clinical remission status were observed at 24 weeks post-treatment. The transplant group had a significantly higher ORR than the conventional group (75.00% vs. 60.71%, χ^2=5.024, P=0.025). Specifically, the CR and PR rates were 33.65% and 41.35% in the transplant group, versus 25.00% and 35.71% in the conventional group, respectively. The NR rate was markedly lower in the transplant group (25.00% vs. 39.29%). These results verified the superior comprehensive therapeutic efficacy of the novel transplant regimen (**Table 7**).

Comparison of safety assessment

The incidence of severe adverse events including infection, liver injury, renal injury and cardiovascular events was comparable between the two groups (all P>0.05). However, significant differences were observed in mild-to-moderate adverse reactions. The transplant group had a higher incidence of drug infusion reactions (15.38% [16/104] vs. 4.46% [5/112], χ^2=7.327, P=0.007). In contrast, the conventional group showed a higher incidence of gastrointestinal reactions (21.43% [24/112] vs. 9.62% [10/104], χ^2=5.674, P=0.017) and hyperglycemia (22.32% [25/112] vs. 3.85% [4/104], χ^2=15.836, P<0.001). Both treatment regimens exhibited acceptable safety profiles with distinct adverse reaction characteristics (**Table 8**).

Analysis of PFS

Kaplan-Meier survival analysis demonstrated that the transplant group had significantly superior PFS compared with the conventional group (**Figure 3**). The median PFS was 28.67

Table 7. Clinical response rates at 24 weeks post-treatment

Parameters	Conventional group (n=112)	Transplant group (n=104)	χ^2	P
OR	68 (60.71%)	78 (75.00%)	5.024	0.025
CR	28 (25.00%)	35 (33.65%)		
PR	40 (35.71%)	43 (41.35%)		
NR	44 (39.29%)	26 (25.00%)		

OR, Overall Remission; CR, Complete Remission; PR, Partial Remission; NR, No Remission.

Table 8. Treatment-related adverse reaction incidence of the subjects

Parameters	Conventional group (n=112)	Transplant group (n=104)	χ^2	P
Infection	16 (14.29%)	11 (10.58%)	0.678	0.410
Hepatic Injury	14 (12.50%)	9 (8.65%)	0.838	0.360
Renal Injury	8 (7.14%)	5 (4.81%)	0.520	0.471
Cardiovascular Event	6 (5.36%)	4 (3.85%)	0.042	0.838
Drug Infusion Reaction	5 (4.46%)	16 (15.38%)	7.327	0.007
Gastrointestinal Reaction	24 (21.43%)	10 (9.62%)	5.674	0.017
Hyperglycemia	25 (22.32%)	4 (3.85%)	15.836	<0.001

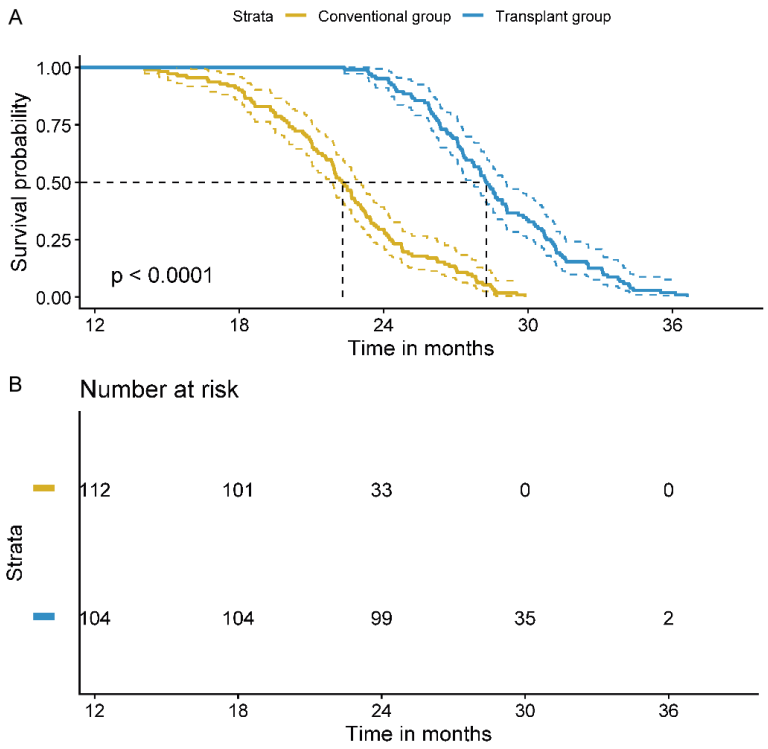

Figure 3. PFS of the subjects. The difference between the two groups was assessed by the log-rank test. A: Kaplan-Meier survival curves; B: Number of patients at risk over time. PFS, Progression-Free Survival.

months (95% CI: 24.12-33.45) in the transplant group and 22.34 months (95% CI: 18.76-26.98) in the conventional group. The log-rank test confirmed a statistically significant difference in PFS between the two groups (P< 0.0001), with sustained separation of survival curves during follow-up.

Multivariate regression analysis for primary outcome

To eliminate the interference of confounding factors, multivariate linear regression analysis was performed with 24-week mRSS as the dependent variable, treatment modality as the independent variable, and all baseline clinical characteristics and baseline organ function indicators as covariates. After full adjustment for confounders, auto-HSCT treatment remained an independent protective factor for reduced 24-week mRSS (β=-7.32, 95% CI: -8.89 to -5.75, P<0.001), further validating the robustness of the primary study findings (**Table 9**).

Discussion

This retrospective cohort study systematically compared the clinical efficacy and safety of a novel rituximab-bendamustine-based AHSCT conditioning regimen versus conventional prednisone combined with cyclophosphamide therapy in refractory SSc patients. The results demonstrate that AHSCT treatment yields superior multisystem organ function improvement and prolonged PFS with a tolerable safety profile, confirming its distinct therapeutic advantages over conventional immunosuppressive therapy.

The most prominent therapeutic benefit of the novel regimen was the significant reduction in

Table 9. Multivariate linear regression analysis for mRSS at 24 weeks

Variable	β coefficient	95% CI	P
Treatment group (Transplant vs. Conventional)	-7.32	-8.89 to -5.75	<0.001
Age (years)	-0.04	-0.12 to 0.04	0.312
Gender (male vs. female)	0.65	-0.78 to 2.08	0.372
BMI (kg/m^2)	-0.11	-0.34 to 0.12	0.342
Living condition (urban vs. rural)	0.23	-1.12 to 1.58	0.738
Education level (high school and below vs. university and above)	0.41	-0.95 to 1.77	0.552
Employment (employed vs. unemployed)	-0.32	-1.68 to 1.04	0.642
Smoking history (yes vs. no)	0.58	-1.05 to 2.21	0.485
Drinking history (yes vs. no)	0.37	-1.34 to 2.08	0.672
Duration of illness (months)	0.02	-0.04 to 0.08	0.488
Anti-Scl-70 positive (yes vs. no)	0.52	-0.89 to 1.93	0.468
ACA positive (yes vs. no)	0.68	-1.02 to 2.38	0.431
Hypertension (yes vs. no)	0.87	-0.56 to 2.30	0.232
Diabetes mellitus (yes vs. no)	0.94	-0.71 to 2.59	0.262
Interstitial lung disease (yes vs. no)	0.22	-1.10 to 1.54	0.742
Baseline mRSS (score)	0.42	0.28 to 0.56	0.001
Baseline FVC (L)	-1.23	-2.01 to -0.45	0.002
Baseline LVEF (%)	-0.08	-0.15 to -0.01	0.032
Baseline eGFR (ml/min/1.73 m^2)	-0.05	-0.12 to 0.02	0.152

Dependent variable: mRSS at 24 weeks. All baseline characteristics listed in **Table 1** were included as covariates. ACA, Anticentromere Antibody; CI, Confidence Interval.

skin thickness. Compared with conventional cyclophosphamide pulse therapy, AHSCT induced faster and more substantial mRSS improvement, which is attributed to the enhanced immunoablation effect of the combined conditioning regimen. Different from the non-specific lymphodepletion of single-agent cyclophosphamide, the addition of rituximab enables targeted depletion of CD20+ B cells, the core effector cells driving SSc-related autoantibody production and profibrotic cytokine (e.g., IL-6) secretion [18, 19]. Bendamustine further eliminates quiescent and dividing lymphocytes and plasma cells, effectively eradicating autoreactive immune clones and suppressing persistent fibrotic signaling [20]. This synergistic anti-autoimmune and anti-fibrotic effect accounts for the superior skin softening efficacy observed in this study, which is superior to that of traditional AHSCT regimens and conventional chemotherapy [21].

Pulmonary involvement is the leading cause of mortality in SSc patients. This study found that the AHSCT regimen significantly improved FVC and DLCO levels and reduced HRCT-confirmed lung lesion severity, indicating its ability to reverse early pulmonary inflammation and delay fibrosis progression. SSc pulmonary fibrosis is driven by persistent infiltration of autoreactive lymphocytes and chronic alveolar injury. The intensive rituximab-bendamustine conditioning regimen efficiently eliminates inflammatory immune cells, interrupts the inflammation-fibrosis vicious cycle, and facilitates lung tissue repair [22, 23]. The improved imaging and functional indicators confirm the regimen's unique value in treating refractory SSc-associated interstitial lung disease, for which limited effective therapies are currently available [24, 25].

The AHSCT regimen also exerted favorable protective effects on cardiac and renal function. The improved LVEF and reduced PASP in the transplant group reflected alleviated myocardial fibrosis and secondary pulmonary hypertension, while the increased eGFR and decreased urinary protein indicated improved scleroderma renal vasculopathy. These multisystem protective effects stem from systemic immune resetting, which reduces autoimmune-mediated endothelial injury and the release of vasoconstrictive and profibrotic mediators, thereby mitigating organ damage caused by persistent immune inflammation [8, 9, 26].

Raynaud's phenomenon and digital ulcers are typical vascular complications of SSc caused by endothelial dysfunction and vasospasm. The significantly lower prevalence of these two manifestations in the transplant group further verified the vascular protective effect of AHSCT. Immune reconstitution after conditioning therapy reduces autoantibody-mediated endothelial damage and regulates vascular tension, thereby improving peripheral microcirculation and reducing ischemic vascular complications [27-29].

The marked reduction in ANA titers in the transplant group provided serological evidence for the regimen's potent immunosuppressive efficacy. The combined rituximab-bendamustine regimen achieves comprehensive depletion of B cell lineages, fundamentally inhibiting autoantibody production and abnormal autoimmune activation. The decreased autoantibody levels are closely correlated with improved clinical manifestations and serve as a reliable biomarker for favorable long-term prognosis in SSc patients [30].

Consistent with objective organ function improvements, patients in the transplant group reported significant enhancements in multiple dimensions of quality of life, especially physical function, pain relief and general health status. This indicates that the multisystem therapeutic efficacy of the novel regimen can be converted into tangible improvements in patients' daily living ability and physical well-being, which is a crucial patient-centered outcome that is often overlooked in clinical trials [31].

The transplant group's higher ORR confirmed the comprehensive therapeutic effect of the novel regimen. More importantly, the significantly prolonged PFS demonstrated that rituximab-bendamustine-conditioned AHSCT can induce sustained disease remission by permanently remodeling the abnormal immune system and delaying the recurrence of autoimmune and fibrotic lesions [9, 32]. This finding highlights the disease-modifying potential of the novel regimen for refractory SSc.

Safety analysis revealed distinct adverse reaction profiles between the two regimens with comparable overall severe adverse event risks. The higher incidence of infusion reactions in the transplant group was mainly related to rituximab administration, which is predictable and manageable with standardized premedication and slow infusion rates. In contrast, the conventional group's higher rates of gastrointestinal toxicity and hyperglycemia were primarily associated with long-term high-dose glucocorticoid exposure, which is avoided in the AHSCT protocol after conditioning. These differential toxicity features provide targeted clinical guidance for individualized treatment selection and patient perioperative management [33, 34].

This study has several limitations. First, the single-center retrospective design may introduce inherent selection bias and limit the generalizability of the findings. Second, the 24-week follow-up period was sufficient for evaluating short-term efficacy and safety but inadequate for assessing long-term outcomes such as late disease relapse, secondary malignancy, and long-term survival benefits. Third, the absence of prospective randomized controlled grouping weakens the level of clinical evidence. Fourth, no detailed immune reconstitution monitoring data were collected, restricting in-depth exploration of the regimen's therapeutic mechanism. Future research should focus on prospective, multicenter, randomized controlled trials to further validate the efficacy and safety of this novel conditioning regimen. Extended long-term follow-up is required to monitor long-term adverse events and sustained therapeutic benefits. Additionally, exploring predictive biomarkers for treatment response and characterizing immune reconstitution patterns after AHSCT will help optimize patient selection and clarify the underlying therapeutic mechanisms. Furthermore, health economic evaluation studies are needed to support the clinical promotion and widespread application of this regimen [35].

Conclusion

In conclusion, this retrospective clinical study confirms that auto-HSCT with a novel rituximab-bendamustine conditioning regimen is a safe and effective therapeutic option for refractory systemic sclerosis. Compared with conventional prednisone plus cyclophosphamide immunosuppressive therapy, this novel regimen achieves superior improvements in skin fibrosis, pulmonary, cardiac and renal organ

lesions, higher clinical remission rates, better patient quality of life, and longer progression-free survival. Although it is associated with a higher incidence of mild, manageable infusion reactions, the risk of severe adverse events is comparable to conventional therapy. These findings support the clinical application of rituximab-bendamustine-conditioned auto-HSCT for the treatment of severe, refractory, progressive SSc. Further prospective controlled studies are warranted to validate its long-term clinical value.

Disclosure of conflict of interest

None.

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