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# Autologous Peripheral Blood Hematopoietic Stem Cell Transplantation for Refractory Systemic Sclerosis and Cancer Patients Undergoing Radiotherapy

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► ***Original article***

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## ABSTRACT

***Background:*** To evaluate the clinical effectiveness of autologous peripheral blood hematopoietic stem cell transplantation (Auto-HSCT) as a therapeutic approach for patients with both refractory systemic sclerosis (SSc) and cancer undergoing radiotherapy. ***Materials and Methods:*** Eleven patients with refractory SSc and concurrent cancer received Auto-HSCT following peripheral blood stem cell mobilization. Standardized radiotherapy protocols were applied based on cancer type. Preconditioning regimens included combinations of cyclophosphamide, melphalan, rituximab, and bendamustine. Post-transplant assessments focused on hematopoietic recovery, SSc disease activity, and tumor response. ***Results:*** A mean of $3.87 \times 10^6$/kg CD34+ cells were collected. All patients achieved hematopoietic reconstitution, with neutrophil and platelet recovery occurring in 9 ± 3 and 14 ± 7 days, respectively. At a median follow-up of 14.6 months, improvements in modified Rodnan skin scores (mRSS), digital ulcers, Raynaud's phenomenon, and pulmonary fibrosis were observed. Eight patients showed sustained improvement in SSc and cancer response. Three patients relapsed and required additional immunotherapy. ***Conclusion:*** Auto-HSCT appears to be a feasible and effective option for patients with both refractory SSc and cancer undergoing radiotherapy. It improved autoimmune disease control, enhanced hematopoietic recovery, and supported cancer treatment with manageable toxicity.

## INTRODUCTION

Systemic sclerosis (SSc), a systemic autoimmune disease, is characterized by microvascular damage, immune dysregulation, and extensive fibrosis of the skin and internal organs, such as the lungs, heart, and kidneys [1, 2]. Patients with refractory SSc face a poor prognosis, with limited treatment options and a 5-year mortality rate exceeding 60% in high-risk cases with diffuse, rapidly progressive disease [3, 4]. Concurrently, cancer patients undergoing radiotherapy often experience significant hematologic toxicity, including bone marrow suppression, which compromises treatment tolerance and increases risks of infections and bleeding [5]. Recent studies confirm the hematopoietic burden of radiation; over 50% of cervical cancer patients receiving chemoradiation develop grade ≥2 hematologic toxicity, linked to bone marrow exposure during radiotherapy [6]. A 2024 Lancet review further emphasized the unmet need for marrow-sparing strategies during radiation therapy, especially in immune-compromised hosts [7]. The coexistence of refractory SSc and cancer in patients undergoing radiotherapy presents a unique clinical challenge, as both conditions contribute to significant morbidity and require innovative therapeutic strategies to address autoimmune activity, tumor progression, and radiotherapy-induced myelosuppression.

Autologous peripheral blood hematopoietic stem cell transplantation (Auto-HSCT) has emerged as a promising approach for managing refractory autoimmune diseases and supporting cancer patients undergoing intensive treatments [8]. By collecting and reinfusing a patient's own CD34+ hematopoietic stem cells, Auto-HSCT facilitates hematopoietic reconstitution, mitigates radiotherapy-induced bone marrow suppression, and modulates immune responses in autoimmune conditions like SSc [9]. Unlike allogeneic transplantation, Auto-HSCT offers a lower risk of complications, such as graft-versus-host disease, making it a safer option for complex cases. Its efficacy has been demonstrated in autoimmune diseases, including SSc, multiple sclerosis, and Crohn's disease, as well as in supporting hematologic recovery in oncology settings [10]. A recent meta-analysis reported that Auto-HSCT significantly improved skin scores, pulmonary outcomes, and survival in patients with SSc, with a transplant-related mortality rate of approximately 6% [11]. Moreover, advancements in transplant protocols-such as cardiac-safe regimens-have enhanced safety even in patients with SSc-related myocarditis [12].

To our knowledge, this is the first study to evaluate Auto-HSCT as a dual-purpose strategy in



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patients with both refractory SSc and concurrent cancer undergoing radiotherapy, aiming to modulate autoimmunity and protect hematopoietic integrity in a single, integrated therapeutic approach.

To evaluate the safety and efficacy of Auto-HSCT in patients with both refractory SSc and cancer undergoing radiotherapy, this study retrospectively analyzed 11 patients treated at the Department of Hematology, Rheumatology, and Oncology of Pu'er People's Hospital from January 2019 to March 2023, assessing its impact on SSc disease activity, tumor response, hematopoietic recovery, and clinical outcomes.

## MATERIALS AND METHODS

### *Clinical data*

Eleven patients diagnosed with both refractory systemic sclerosis (SSc) and cancer, all undergoing radiotherapy, were enrolled at the Department of Hematology, Rheumatology, and Oncology of Pu'er People's Hospital from January 2019 to March 2023. All patients met the 2013 American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) classification criteria for SSc [13]. The cohort included 8 females and 3 males, with a mean age of 46.5 years (range: 32–61). Cancer types included breast cancer (4 patients), lung cancer (3), lymphoma (2), esophageal cancer (1), and pancreatic cancer (1). SSc-related complications included interstitial lung disease (7 patients), arthritis (6), digital ulcers (4), overlapping systemic lupus erythematosus with hemophagocytic syndrome (1), rheumatoid arthritis (1), and penile atrophy (1). Detailed baseline characteristics are summarized in table 1. The modified Rodnan skin score (14)(mRSS) before transplantation was >25 points, indicating severe skin involvement. All patients had received standardized immunosuppressive therapy (e.g., cyclophosphamide, azathioprine, or mycophenolate mofetil) for SSc and/or chemotherapy for cancer for over six months prior to enrollment, with poor response (persistent mRSS elevation, worsening skin fibrosis, esophageal involvement, Raynaud's phenomenon, non-healing fingertip ulcers, and/or progressive tumor activity). High-resolution computed tomography (HRCT) confirmed persistent pulmonary interstitial fibrosis in SSc cases. Exclusion criteria included active tuberculosis, acute or chronic hepatitis (A, B, or C), severe cardiac, pulmonary, or renal dysfunction, active bacterial or fungal infections, pregnancy, or lactation.

**Table 1.** Detailed characteristics of patients enrolled in the study.

| Case | Age (years) | Sex | Cancer Type | SSc Subtype / Overlap | Baseline mRSS | Preconditioning Regimen | Follow-up (months) |
|---|---|---|---|---|---|---|---|
| **1** | 45 | F | Breast | dcSSc + PBC | 32 | RTX + Benda + CTX | 28 |
| **2** | 48 | F | Lymphoma | dcSSc + SLE + HLH | 32 | Mel + Benda | 28 |
| **3** | 42 | M | Lung | dcSSc | 32 | Mel | 28 |
| **4** | 40 | F | Breast | dcSSc | 28 | RTX + Benda + CTX | 36 |
| **5** | 43 | M | Lung | dcSSc | 28 | Mel + Benda | 30 |
| **6** | 54 | F | Esophageal | dcSSc | 32 | Mel + CTX | 18 |
| **7** | 46 | F | Lymphoma | dcSSc + RA | 32 | Mel + Benda | 14 |
| **8** | 39 | F | Breast | dcSSc | 40 | CTX | 14 |
| **9** | 37 | F | Breast | dcSSc | 28 | CTX | 12 |
| **10** | 52 | M | Lung | dcSSc | 32 | Mel | 12 |
| **11** | 61 | M | Pancreatic | dcSSc | 32 | CTX | 6 |

Abbreviations: mRSS = modified Rodnan skin score; dcSSc = diffuse cutaneous systemic sclerosis; PBC = primary biliary cholangitis; SLE = systemic lupus erythematosus; HLH = hemophagocytic lymphohistiocytosis; RA = rheumatoid arthritis; RTX = rituximab; Benda = bendamustine; CTX = cyclophosphamide; Mel = melphalan.

### *Radiotherapy protocol*

Radiotherapy was administered based on cancer type and stage, following standard oncology guidelines. Patients with breast cancer received external beam radiotherapy (EBRT) with a total dose of 50–60 Gy in 1.8-2.0 Gy fractions over 5-6 weeks. Lung cancer patients received stereotactic body radiotherapy (SBRT) for early-stage disease (50-60 Gy in 3–5 fractions) or conventional EBRT for advanced stages (60-66 Gy in 2.0 Gy fractions). Lymphoma patients underwent involved-site radiotherapy (ISRT), while patients with other solid tumors received EBRT tailored to tumor size and location.

All radiotherapy was performed using a Varian TrueBeam® linear accelerator (Varian Medical Systems, Palo Alto, USA). Treatment planning was conducted with the Eclipse™ Version 16.1 software (Varian Medical Systems), incorporating CT-based 3D conformal or intensity-modulated radiotherapy (IMRT) protocols. Daily image-guided radiotherapy (IGRT) was employed to ensure precision.

### *Mobilization strategy*

Peripheral blood stem cell mobilization was performed using cyclophosphamide (CTX) at 2.0 g/m$^2$ intravenously for 2 days, followed by recombinant human granulocyte colony-stimulating factor (G-CSF) at 10 μg/kg/day subcutaneously for 4 days when white blood cell counts began to recover post-nadir. Plerixafor (Mozobil) at 0.24 mg/kg was administered subcutaneously 11 hours before collection. Stem cell collection proceeded when white blood cell counts exceeded 5 × 10$^9$/L and platelet counts exceeded 50 × 10$^9$/L, targeting ≥2 × 10$^6$/kg CD34+ cells and ≥5 × 10$^8$/kg mononuclear cells (MNC). Collected cells were



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cryopreserved in a -80°C freezer using a preservation solution.

All apheresis procedures were performed using the COBE Spectra system (Terumo BCT, USA), and cryopreservation used CryoMACS® freezing bags (Miltenyi Biotec, Germany). Cyclophosphamide, melphalan, and bendamustine were sourced from Baxter (USA); rituximab from Roche (Switzerland); plerixafor from Sanofi (France); and G-CSF from Kyowa Kirin (Japan).

### *Preconditioning regimens*

Patients received one of the following preconditioning regimens: four patients received rituximab (375 mg/m$^2$ on day -8), bendamustine (90 mg/m$^2$ on days -7 to -6), and CTX (50 mg/kg on days -5 to -2); six patients received melphalan (Mel)-based regimens (three with Mel at 70 mg/m$^2$ on day -3 alone, two with Mel at 70 mg/m$^2$ on day -3 plus bendamustine at 90 mg/m$^2$ on days -5 to -4, and one with Mel at 70 mg/m$^2$ on day -3 plus CTX at 50 mg/kg on days -7 to -4); one patient received CTX alone (50 mg/kg on days -5 to -2).

### *Supportive Care and Complication Prevention*

One week prior to entering the laminar flow ward, patients initiated oral levofloxacin and trimethoprim-sulfamethoxazole for gut decontamination, shaved body hair, and underwent a 1:2000 chlorhexidine bath. A peripherally inserted central catheter (PICC) was placed in the elbow vein before ward entry. Following high-dose CTX, mesna was administered to prevent hemorrhagic cystitis. Platelet transfusions were provided when counts fell below 20 × 10$^9$/L or during active bleeding, and red blood cell transfusions were given when hemoglobin was <60 g/L. G-CSF (5 μg/kg) was administered 2 days post-Auto-HSCT to promote hematopoietic reconstitution. Broad-spectrum antibiotics were used for infections associated with granulocytopenia.

### *Post-transplant monitoring*

Post-transplant assessments included hematopoietic reconstitution (time to neutrophil [ANC] >0.5 × 10$^9$/L and platelet [PLT] >20 × 10$^9$/L), SSc disease activity (via mRSS), tumor response (per RECIST criteria for solid tumors or relevant hematologic response criteria), clinical symptoms (e.g., skin fibrosis, Raynaud's phenomenon, digital ulcers), and laboratory indicators (e.g., antinuclear antibody [ANA] titer, anti-SCL-70 antibody, and tumor markers). Evaluations were conducted at 3-, 4-, and 6-months post-transplantation, and then every 6 months as needed. The median follow-up duration was 14.6 months (range: 6–36 months).

### *Statistical analysis*

Data were analyzed using SPSS 26.0 (IBM Corp., Armonk, NY, USA). Quantitative data were expressed as mean ± standard deviation. Categorical data were reported as frequencies and percentages. Comparisons before and after transplantation were performed using paired t-tests or Wilcoxon signed-rank tests, depending on data distribution. Confidence intervals (95% CI) were calculated for key outcomes (e.g., mRSS, tumor response). A p-value < 0.05 was considered statistically significant.

### *Ethics*

This study was approved by the Ethics Committee of Pu'er People's Hospital (Ethics Approval No.: SKJJ-2024-02) and conducted in accordance with the Declaration of Helsinki. The study was formally registered on March 12, 2024. All patients provided written informed consent prior to participation.

## RESULTS

### *Mobilization and collection of peripheral blood stem cells*

All patients successfully underwent stem cell mobilization and collection. G-CSF was initiated 6–10 days after CTX in all 11 patients. Collection was completed in one session for 3 patients, two sessions for 7 patients, and three sessions for 1 patient. The median mononuclear cell (MNC) yield was 5.91 × 10$^8$/kg (range: 3.5–8.0 × 10$^8$/kg), and the median CD34+ cell count was 3.87 × 10$^6$/kg (range: 1.5–5.4 × 10$^6$/kg).

### *Hematopoietic reconstitution*

All patients achieved prompt hematopoietic recovery following Auto-HSCT. The median neutrophil recovery time (ANC >0.5 × 10$^9$/L) was 9 ± 3 days, and the median platelet recovery time (PLT >20 × 10$^9$/L) was 14 ± 7 days.

### *Radiotherapy outcomes*

Radiotherapy resulted in favorable tumor responses in most patients. Among breast cancer cases (n=4), 3 achieved partial response (PR) and 1 had stable disease (SD). Among lung cancer patients (n=3), 2 achieved complete response (CR) with SBRT, and 1 had PR after EBRT. Both lymphoma patients achieved CR. Among other cancers, 1 (esophageal) had PR, and 1 (pancreatic) had SD. Figure 1 shows response distribution across tumor types.

Radiotherapy-related toxicities were manageable: grade 1–2 erythema (n=6), mild fatigue (n=8), and grade 1 mucositis (n=3). No grade 3–4 adverse events were reported.

### *Effectiveness on systemic sclerosis and clinical improvement*

Post-transplant follow-up revealed significant improvement in SSc symptoms and biomarkers. At 3 and 6 months, mean mRSS decreased by 18 ± 5



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points. Clinical symptoms such as skin thickening, Raynaud's, and digital ulcers improved in most patients. Table 2 summarizes key changes in mRSS and tumor response.

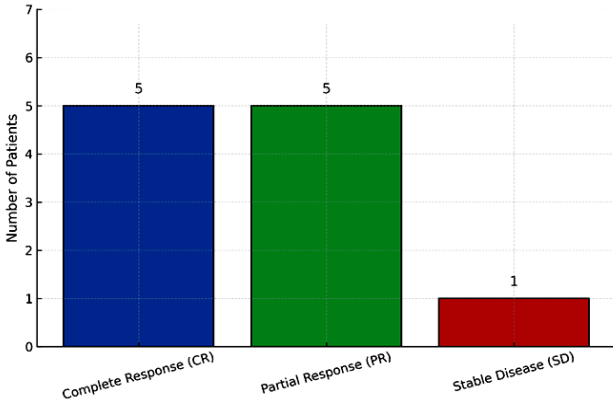


**Figure 1.** Tumor response after radiotherapy (n=11). CR = 5 patients (45.5%), PR = 5 patients (45.5%), SD = 1 patient (9.1%) Abbreviations: CR = complete response; PR = partial response;

**Table 2.** Pre- and post-transplant SSc and tumor response summary.

| Case | Baseline mRSS | mRSS at Follow-Up | Tumor Response | Outcome Description |
|---|---|---|---|---|
| **1** | 32 | 14 | PR | SSc improved, GGO resolved, breast tumor stable |
| **2** | 32 | 6 | CR | HLH/SLE remission, lymphoma response |
| **3** | 32 | 9 | CR | Lung CR, mRSS drop |
| **4** | 28 | 13 | PR | Skin score improved, tumor stable |
| **5** | 28 | 9 | CR | Lung CR, SSc resolved |
| **6** | 32 | 6 | PR | SSc and esophageal tumor both improved |
| **7** | 32 | 20 | CR | RA and SSc stable, lymphoma CR |
| **8** | 40 | 6 | PR | SSc resolved, tumor stable |
| **9** | 28 | 6 | SD | SSc mild improvement, breast cancer stable |
| **10** | 32 | 6 | CR | Lung CR, SSc improved |
| **11** | 7 → 28 | 28 | PD | Relapse of SSc and cancer |

Abbreviations: mRSS = modified Rodnan skin score; CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; GGO = ground-glass opacity; HLH = hemophagocytic lympho-histiocytosis; SLE = systemic lupus erythematosus; RA = rheumatoid arthritis; SSc = systemic sclerosis.

### *Safety*

No transplant-related deaths or organ failures were observed. Gastrointestinal symptoms (nausea, vomiting, diarrhea) occurred in all patients and resolved with symptomatic care. Febrile episodes occurred in 8 patients: 7 due to bacterial infections and 1 due to COVID-19 pneumonia, resolved after convalescent plasma therapy. Thrombocytopenia occurred in all patients; 7 required platelet transfusions. No red cell transfusions or organ toxicity occurred during follow-up.

## DISCUSSION

Systemic sclerosis (SSc) remains a challenging autoimmune condition, particularly in its diffuse cutaneous form (dcSSc), which is associated with progressive fibrosis, immune dysregulation, and high mortality. Standard immunosuppressive therapies frequently fail in refractory cases, highlighting the urgent need for novel treatment strategies [7, 15-18]. Concurrently, patients with cancer undergoing radiotherapy often experience hematologic toxicity, particularly bone marrow suppression, which increases treatment-related morbidity and mortality [19]. The co-occurrence of refractory SSc and malignancy presents a unique therapeutic dilemma that demands a multidisciplinary approach capable of addressing immune overactivation, tumor progression, and myelosuppressive complications of radiotherapy.

Autologous peripheral blood hematopoietic stem cell transplantation (Auto-HSCT) has been established as an effective treatment for autoimmune diseases, including SSc, and a supportive modality in oncology for hematologic recovery during cytotoxic therapies [20-22]. In our retrospective study of 11 patients with concurrent refractory SSc and cancer receiving radiotherapy, Auto-HSCT demonstrated dual benefit in improving autoimmune disease control and supporting radiotherapy outcomes. All patients achieved successful hematopoietic recovery with acceptable safety profiles, and eight patients exhibited sustained improvements in SSc clinical and serologic parameters. These results are consistent with prior large trials such as the ASTIS and SCOT studies, which demonstrated significant reductions in mRSS scores and improved event-free survival in dcSSc patients undergoing Auto-HSCT compared to cyclophosphamide therapy alone [23, 24]. Importantly, our study contributes novel insights by applying Auto-HSCT in patients undergoing radiotherapy for solid and hematologic malignancies. Patients receiving radiotherapy showed partial or complete tumor responses in most cases, with no grade 3 or higher radiation toxicities. This supports Auto-HSCT's role in mitigating hematologic side effects of radiotherapy, a finding also seen in Auto-HSCT-supported oncology settings [25-27]. The absence of transplant-related mortality or organ toxicity in our study is notable given the historically high risks associated with Auto-HSCT in SSc, particularly with myeloablative regimens. This favorable safety profile may be attributed to the use of non-myeloablative conditioning in our cohort, consistent with the ASSIST trial and reinforced by international studies [28, 29]. The therapeutic mechanisms of Auto-HSCT likely involve immune reset through depletion of autoreactive lymphocytes and reconstitution of a self-



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tolerant immune system, alongside hematopoietic recovery that permits uninterrupted cancer treatment [30]. This dual mechanism is supported by our observation of improvement not only in mRSS and autoantibody profiles but also in overlap syndromes and stabilization of interstitial lung disease (ILD). The limited response in usual interstitial pneumonia (UIP) versus nonspecific interstitial pneumonia (NSIP) cases is consistent with previous evidence showing better outcomes in inflammatory rather than fibrotic ILD phenotypes [31]. Another relevant observation is the apparent advantage of rituximab-based preconditioning regimens. Patients receiving rituximab in combination with bendamustine and cyclophosphamide showed no disease relapse, supporting evidence for B-cell depletion as a potentiator of Auto-HSCT efficacy in SSc [32]. Conversely, patients receiving melphalan-based regimens or cyclophosphamide alone were more likely to relapse, suggesting the importance of regimen intensity and immune modulation. Our study has several limitations that warrant consideration. The small sample size (n = 11) and retrospective design limit generalizability and preclude robust statistical inference. Heterogeneity in cancer types, Auto-HSCT protocols, and timing of radiotherapy introduces confounding factors. Although some patients had follow-up periods extending to 36 months, the median follow-up duration of 14.6 months may not capture long-term relapse or late complications. The concurrent administration of radiotherapy and stem cell mobilization also limits the ability to isolate individual effects. Nonetheless, these limitations are offset by the novelty of our approach and the consistent internal results across patients. In conclusion, our findings suggest that Auto-HSCT may serve as a comprehensive treatment strategy for patients with coexisting refractory SSc and cancer undergoing radiotherapy. The observed improvements in disease activity, tumor response, and hematologic recovery support its dual utility. Further prospective, controlled studies with standardized conditioning regimens and longer follow-up are essential to confirm these findings and define best practices for this complex patient population.

## CONCLUSION

Autologous peripheral blood hematopoietic stem cell transplantation appears to be a safe and effective therapeutic option for patients with refractory systemic sclerosis undergoing radiotherapy for cancer. It offers dual benefits in immune modulation and hematologic recovery. While promising, these findings warrant validation in larger, controlled studies to optimize protocols and confirm long-term outcomes.

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***Ethical considerations***: This study was approved by the Ethics Committee of Pu'er People's Hospital (Ethics Approval No.: SKJJ-2024-02) and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

***Author contributions***: Tong Sifan, Liu Zhenghai, Wen Qin: data collection, statistical analysis, interpretation of results, and drafting of the manuscript. Zhang Xi, Zheng Chaoen: conceptualization, study design, critical revision for intellectual content, supervision, and acquisition of funding. Other co-authors: contributed to data acquisition, clinical follow-up, and research support.

***AI usage***: Authors declare that they did not use AI for preparation of the manuscript except for language editing.

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