The burning question: To use or not to use cyclophosphamide in systemic sclerosis
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Abstract
Fibrosis, inflammation, and vasculopathy are the main determinants of systemic sclerosis (SSc) pathogenesis. Cyclophosphamide (CYC), an alkylating agent, has been used to treat skin fibrosis and interstitial lung diseases in SSc for many years and still represents a mainstay in hematopoietic stem cell transplantation. Despite significant effect in reducing lung functional impairment and skin tightness, CYC has a significant safety burden, including infection risk and bone marrow and bladder toxicity. Moreover, it can affect fertility and also cause a predisposition for cancer development in the future, particularly in the bladder. This review summarizes the current evidences regarding the use of CYC to treat SSc, its efficacy and safety profile, and currently available or tested alternative drugs for lung and skin involvement in SSc.

Keywords: Systemic scleroderma, cyclophosphamide, interstitial lung disease, skin, fibrosis

Introduction
Systemic sclerosis (SSc) pathogenesis is characterized by the simultaneous presence of inflammatory, fibrotic, and vasculopathic features. Endothelial damage leads to endothelial-to-mesenchymal transition (1), which contributes to fibroblast proliferation, extracellular matrix proliferation, and collagen deposition. Autoimmune processes and cellular infiltration affect both vascular and fibrotic pathways, thereby providing a proinflammatory and profibrotic environment (1).

Endothelial damage may be the first pathological change in SSc. This is followed by vasculopathy, vascular instability, slow vascular obliteration, and thrombosis. The clinical downstream of these changes includes the Raynaud’s phenomenon, digital ulcers, secondary traumatic ulcers, gangrene, and even digital amputation. The vascular changes can include pulmonary hypertension, scleroderma renal crisis, gastrointestinal vascular ectasia and bleeding, peripheral neuropathy, myopathy with weakness, and myocardial infarction.

As an example, one of the first manifestations of SSc is Raynaud’s phenomenon, which is the first symptom in 90%-95% of patients. Despite its vascular origin, Raynaud’s phenomenon is usually associated with edematous inflammatory infiltration of the fingers, also called “puffy hands” (2). Inflammatory cellular infiltration and subsequent collagen production can appear in essentially any other parts of the skin. The distribution of fibrotic involvement can be limited (distal to knees and neck) or diffuse (if also proximal to the aforementioned sites), or in 3%-5% of patients, it may be absent from the skin (3).

Interstitial lung disease (ILD) is an important fibrotic complication occurring in 40%-70% of patients and leading to progressive functional impairment and dyspnea; it can result in progressive disability and death (4). Collagen deposition can also appear in the heart and pericardium, leading to cardiomyopathy, MI, and arrhythmia; however, it is not often clinically apparent, occurring in only 3%-9% of patients (5, 6). In the gastrointestinal tract where collagen deposition is seen in 70%-85% of patients, it can result in multiple manifestations associated with dysmotility, bleeding, and malabsorption (7). In the kidney, it may be seen as proteinuria or renal insufficiency or as systemic hypertension, although its frequency as a pure manifestation of SSc is controversial, and its frequency ranges from 5% to 45% (8). In the peripheral muscles and joints, fibrosis can cause weakness, joint pain, and disability (9).

Cyclophosphamide (CYC) acts as a potential alkylating and nonspecific immunosuppressive agent causing cellular death of both resting and dividing B and T lymphocytes. This results in cellular depletion...
and suppression and can result in decrease in antibodies (10). Given its good absorption,CYC can be administered either orally or intravenously in different cumulative dosages. The daily oral administration usually targets 2 mg/kg of body weight, and the monthly intravenous route usually ranges from 500 to 1,000 mg/m² of body surface. Both regimens are usually for 12 months and are subsequently followed by a “drug holiday” or maintenance with an immunosuppressive agent with fewer or less severe side effects. CYC is one of the mainstays in the treatment of SSc and is part of the European League Against Rheumatism recommendations. Based on the 2015 recommendations, CYC represents the first-line choice for the treatment of ILD and is one of the options for the treatment of diffuse skin involvement (11). Moreover, it is part of the 2 principle regimens for hematopoietic stem cell transplantation (HSCT) in which high CYC doses are employed for both mobilization and conditioning phases (10).

Clinical and research consequences

**CYC in SSc-ILD**

CYC was used in the treatment arm in 2 randomized clinical trials, namely Scleroderma Lung Studies (SLS) I and II (12, 13). Both the studies included patients with SSc-ILD with evidence of active lung involvement: inflammation of bronchoalveolar lavage fluid or ground glass opacities observed on high-resolution computed tomography (HRCT). Lung involvement was limited to mild-to-moderate impairment of forced vital capacity (FVC%) in SLS I and stabilized up to month 24 in SLS II; this resulted in a prevalence of “improvers” (defined as improved predicted FVC% predicted by ≥0.1%) ranging from 49.3% in SLS I to 64.7% in SLS II.

Conversely, no statistically significant improvement was found in DLCO% (14). A reduction in the extent of ILD features was observed in the CYC groups using HRCT (measured by a quantitative texture analysis using dedicated software). The quantitative change in HRCT correlated statistically with the changes in FVC%, DLCO%, and dyspnea index (15).

**CYC in diffuse SSc**

CYC was used among others in the treatment arms of the prospective observational European Scleroderma Observational Cohort study; the protocol enrolled 326 patients with early diffuse (within 3 years from the onset of skin tightness) SSc between 2010 and 2014 and followed them up for 24 months (16). The patients were treated with 1 of the following 4 regimens: (i) 25 mg/weekly methotrexate, (ii) up to 2,000 mg MMF per day, (iii) CYC 1-2 mg/kg/day orally for 12 months or 500 mg/m² intravenous CYC monthly for 6-12 months, and (iv) no immunosuppressive drugs. Current administration of steroids was allowed (16). Change in the modified Rodnan skin score (mRSS) over time was the primary end point, and FVC%, DLCO%, and quality of life assessed using the Health Assessment Questionnaire Disability Index; hand functionality assessed using the Cochin Hand Functional Scale; and survival status were the main secondary outcomes. The CYC groups had more active severe disease at baseline, defined by a higher prevalence of ILD or cardiac involvement and more severely impaired hand functionality. The median change in mRSS at 12 months was -3.3 (-4.9 to -1.7) units in the CYC group, which was not statistically significantly different from the other 3 treatment arms. FVC% and DLCO% change also did not differ among the treatment groups. When considering only the patients with HRCT-confirmed presence of ILD, the CYC-treated patients demonstrated +7.4% absolute increase in FVC% predicted versus +2.0% for methotrexate, +3.2% for MMF, and +4.0% for the nonimmunosuppressive treatment group (16). This is not statistically different but might be interpreted as a numerical difference in favor of CYC.

In both the SLS studies, the mRSS values were recorded in all the patients both with limited and diffuse SSc. Patients with diffuse cutaneous SSc (total 84 patients combining both the studies) exhibited a progressive reduction in mRSS, which was more significant during the treatment period than in the year of follow-up and showing a statistically significant correlation with higher mRSS at the baseline (14). No significant mRSS change was seen in patients with limited SSc because there was a possible floor effect.

**CYC in autologous HSCT for diffuse SSc**

HSCT has an immunological rationale for the treatment of autoimmune conditions. According to its protocol, CYC engenders a profound ablative effect on T cells, which is “rescued” by stem cell reinfusion that regenerates a new immunological repertoire (17). Both the mobilization and the conditioning phase of the transplantation procedure use CYC as a pharmacological mainstay together with antithymocyte globulin (ATG). Two different HSCT protocols are presently used: the “immunoablative” protocol, which uses higher doses of CYC and lower doses of ATG and the “myeloablative” protocol, which uses lower doses of CYC and higher doses of ATG, along with a moderate dose of total body irradiation with gonadal and pulmonary shielding.

The Autologous Stem cell Transplantation International Scleroderma (ASTIS) trial was a phase III study applying the immunosuppressive protocol in 79 patients with SSc. In the HSCT arm, about 200 mg/kg intravenous CYC over 4 days was administered for mobilization followed by 4 g/m² CYC administration for conditioning. This was followed by reinfusion of selected hematopoietic stem cells that have previously undergone leukapheresis. This “immunoablative” regimen was compared with 750 mg/m²/month CYC intravenous administration for 12 months (18). Similarly, in the phase III Scleroderma: Cyclophosphamide or Transplantation (SCOT) trial performed a “myeloablative” HSCT procedure using 120 mg/kg of CYC for mobilization in 33 patients versus CYC 500 mg/m² for the first month followed by 750 mg/m² for 11 months in 37 patients with SSc (19). Both the studies considered survival status and event-free survival for major organ involvement by following up the patients for 24 months. The control group, whereas SLS II used up to 3 g/day of mycophenolate mofetil (MMF) for 24 months in the control group. In both the CYC cohorts, a significant improvement was observed in the FVC% compared to the baseline values starting at month 3 and peaking at month 18. It regressed by month 24 in SLS I and stabilized up to month 24 in SLS II; this resulted in a prevalence of “improvers” (defined as improved predicted FVC% predicted by ≥0.1%) ranging from 49.3% in SLS I to 64.7% in SLS II.

Conversely, no statistically significant improvement was found in DLCO% (14). A reduction in the extent of ILD features was observed in the CYC groups using HRCT (measured by a quantitative texture analysis using dedicated software). The quantitative change in HRCT correlated statistically with the changes in FVC%, DLCO%, and dyspnea index (15).

**Main Points**

- Systemic sclerosis pathogenesis includes an inflammatory autoimmune cellular component.
- Cyclophosphamide immunosuppressive effect is beneficial for both skin and lung involvement in systemic sclerosis.
- Cyclophosphamide safety profile includes cytopenia, fertility and malignancy issues.

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months in the ASTIS trial and for 54 months in the SCOT trial. Both the studies confirmed a statistically significant superiority of HSCT over CYC on both survival status and event-free survival for major lung, heart, or kidney involvement (18, 19), despite the higher burden of treatment-related mortality in the HSCT group (17). In accordance with the usual approach in HSCT studies, which does not include a placebo arm, neither HSCT studies had a placebo arm. In addition, it should be noted that the dose of CYC used as part of the HSCT arm was lower in the SCOT trial than that in the ASTIS trial (10).

**CYC in other SSc organ involvement**

Gastric antral vascular ectasia (GAVE) represents a form of gastrointestinal organ involvement in SSc, sometimes causing bleeding and requiring a prompt medical and/or surgical intervention (7). Case reports described the use of intravenous CYC in patients with GAVE refractory to conventional endoscopic approaches. The dosages ranged from 700 to 1,000 mg monthly for 5-9 months with some reported success in preventing recurrence. Some consider this data as the basis for a possible rescue treatment for this complication (20).

**CYC: Is it a safety profile?**

CYC, an alkylating agent, has a significant toxicity that limits its use to relatively short periods and limited cumulative dosage. Data from the SLS I study showed a higher incidence of total adverse events (AEs) in the CYC group, with specific statistical significance for hematological AEs, mostly leukopenia (26% versus 2%, p<0.001) during the first year, but no increase in the infections (21); however, a perceived increased risk of infection persists.

Given the urinary clearance of CYC metabolites, CYC possesses bladder toxicity. This may manifest as hematuria and is correlated with an increased risk of bladder cancer after 4-5 years. A review including patients with different rheumatic conditions (vasculitis, systemic lupus erythematosus, rheumatoid arthritis, and scleroderma) treated with CYC showed a 12%-41% incidence of hemorrhagic cystitis in patients with long-term high-dose exposure to oral CYC (>30 months and >100 g total cumulative treatment). Hematuria is predictive of an increased risk of bladder cancer after 5 years (22). This increased risk was not seen for intravenous CYC administrations, being related to usually lower cumulative dosages and the concomitant administration of mesna and fluids (22).

Although hematuria occurred in about 9.9% of the CYC arm patients in the SLS I study, there was only 1 case of in situ bladder cancer during the 2 years of study observation. Globally, all types of cancers reached 4.7% incidence with 2 more events after the second year in patients exposed to oral CYC (21). Compared to the abovementioned literature data, this incidence is low, possibly related to the lower CYC cumulative dosage compared to that in the observational datasets.

Fertility counseling is a priority when using CYC. In a small survey among female rheumatic diseases patients treated for their condition, amenorrhea, nulliparity, and infertility were more common in patients exposed to CYC during their fertile age compared to the non-exposed patients, with a possible protective effect of gonadotropin-releasing hormone agonist supplementation during the treatment (23). The negative effect of CYC on fertility was even more significant (close to 50% incidence) in patients exposed to HSCT (24).

**Conclusion**

**CYC: Should it still be used?**

Various drugs have been tested in the last 10-15 years showing promising results in patients with SSc (25). MMF is presently considered the first-line choice for the treatment of diffuse SSc skin involvement and ILD (4). MMF was used as the comparator group in the SLS II study, with target dosage of 3 g/day according to tolerance. In that study, MMF and CYC were equally effective in improving the FVC% or preventing its decline (26). A post-hoc analysis comparing the MMF group from SLS II and the placebo group from SLS I showed that 2 years of treatment with MMF statistically significantly improved FVC%, DLCO%, and dyspnea index compared to those in the placebo group (13).

mRSS in both SLS I and II studies demonstrated statistically significant improvement after both CYC and MMF administration, being more significant in patients with diffuse SSc (85.2% and 77.7% improvers, respectively, defined as ≥-1 mRSS unit decline) when compared with placebo administration (27).

MMF was generally better tolerated than CYC; however, the differences were surprisingly low. There was a lower rate of premature discontinuation, a trend for longer time before drug withdrawal, and better adherence to the target dose in the MMF group. There was also a significantly lower incidence of leukopenia and thrombocytopenia; however, there was no increased infection or bleeding. Finally, there was a statistically significant involuntary weight loss among patients treated with CYC, although its cause was not clear (26).

Reports have shown a potential role for rituximab for the treatment of both skin fibrosis and ILD. An analysis of the observational European Scleroderma Trials and Research group cohort recently compared 254 rituximab-treated patients and 9,575 non-rituximab-treated patients; this analysis showed an overall good safety profile with 14% and 17% incidence of non-severe and severe AEs, respectively. Moreover, the mRSS decline was significantly higher in the rituximab-treated group when the drug was primarily indicated for skin involvement, with higher chances of improvement in skin thickness (p=0.002). This supports the previous data on patients whose skin improved after treatment with rituximab in which there was a clear decrease in skin collagen (28). No significant difference in FVC% or DLCO% worsening was found between the 2 groups; however, a numerically positive trend was noted when rituximab was administered in combination with MMF for ILD indication (29). Considering these and other previous promising results, an ongoing study is recruiting patients with connective tissue disease-related ILD, including SSc, comparing 1,000 mg rituximab given at baseline for 2 weeks versus 600 mg/m² body surface of monthly intravenous CYC for 6 months. Absolute change in the FVC% at 48 weeks is the primary end point, and change in DLCO%, quality of life, progression-free survival, and safety are the secondary outcomes (30).

Given the recent approval of antifibrotic drugs for idiopathic pulmonary fibrosis, 2 compounds are being evaluated for the treatment of SSc-ILD on the hypothesis of a complementary antifibrotic effect in addition to the immunosuppressive and anti-inflammatory effects of MMF or methotrexate (25).

Pirfenidone (target dose of 800 mg TID) combined with MMF (target dose of 1,500 mg BID) versus MMF alone are the 2 treatment arms of the SLS III study. SLS III, a clinical trial, is a double-blind randomized study currently enrolling up to 150 patients with SSc-ILD in the United States, with change in the FVC% as the primary end point and change in DLCO%, mRSS, and dyspnea and quality of life indexes as the secondary outcomes (31). With a similar pharmacodynamic hypothesis, nintedanib (150 mg
BID) is being tested against placebo in 520 patients with SSC-ILD on a stable background immunosuppressive standard-of-care treatment. These patients can be on stable MMF or methotrexate as background therapy with a stable dose of steroids ≤10 mg prednisone equivalent per day. The primary end point is 52-week FVC% decline, and change in mRSS and Saint George Respiratory Questionnaire are the main secondary outcomes. The study data collection was completed on November 28, 2018, and the results from the SENSCIS trial are awaited (32, 33).

Considering all these data, despite the important role CYC has played in the previous decades and the pivotal role it exerts in the HSCT procedure, an attractive alternative treatment option is available. These data support the use of MMF as the first-line treatment in diffuse skin involvement and ILD. Other options are being tested in randomized clinical trials or in multicenter observational collaborations including rituximab or antifibrotic agents (pirfenidone and nintedanib). CYC will undoubtedly remain as an alternative second-line treatment, in case of persistent disease activity and progression, as part of HSCT in patients who may not respond to standard-of-care treatment, or a possible rescue treatment for severe complications, such as GAVE.

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