CONCISE COMMUNICATION

Successful use of intravenous cyclophosphamide pulse therapy for interstitial lung disease in a patient with systemic sclerosis on hemodialysis

Takehiro TAKAHASHI,1 Yoshihide ASANO,1 Ryo SUNAGA,1 Yohei ICHIMURA,1 Takashi TANIGUCHI,1 Mizuho YAMAMOTO,1 Zenshiro TAMAKI,1 Tomonori TAKEKOSHI,1 Hiroshi MITSUI,1 Makoto SUGAYA,1 Takamoto OHSE,2 Shinichi SATO1

1Department of Dermatology, and 2Division of Nephrology and Endocrinology, University of Tokyo Graduate School of Medicine, Tokyo, Japan

ABSTRACT

Interstitial lung disease and scleroderma renal crisis are major complications of systemic sclerosis, which occasionally coexist in patients with the diffuse cutaneous subtype. We herein report a case of diffuse cutaneous systemic sclerosis under hemodialysis due to a previous history of scleroderma renal crisis, whose interstitial lung disease was effectively and safely treated with a half dose of i.v. cyclophosphamide pulse. The dose of cyclophosphamide and the timing of hemodialysis leading to efficacy and low toxicity are discussed.

Key words: hemodialysis, interstitial lung disease, intravenous cyclophosphamide pulse, scleroderma renal crisis, systemic sclerosis.

INTRODUCTION

Systemic sclerosis (SSc) is a multisystem autoimmune disease characterized by vasculopathy and fibrosis of the skin and certain internal organs. Interstitial lung disease (ILD) is a major visceral involvement determining the prognosis of SSc, especially diffuse cutaneous SSc (dcSSc), as well as pulmonary arterial hypertension.1 Thus far, the combination therapy of prednisone with intravenous cyclophosphamide pulse (IVCY) is the first-line treatment and has been widely used against ILD associated with SSc.2 Scleroderma renal crisis (SRC) is another important vascular complication mainly observed in patients with early dcSSc. After the emergence of angiotensin-converting enzyme inhibitors, the prognosis of SRC has been dramatically improved,3 but the delayed diagnosis and treatment often result in induction of hemodialysis (HD). Because SRC mostly occurs in patients with early progressive dcSSc, this complication often coexists with ILD. Therefore, it appears not to be rare to administrate IVCY to SSc-ILD patients under HD due to the previous history of SRC. However, to the best of our knowledge, there has been no report regarding IVCY therapy on SSc-ILD patients under HD. We herein report a case of SSc-ILD under HD due to a past history of SRC, who was successfully treated with a half dose of IVCY. We also discuss the dose of cyclophosphamide and the timing of HD leading to efficacy and low toxicity of IVCY.

CASE REPORT

A 63-year-old woman without any remarkable past medical history was referred to our hospital in November 2009 for the treatment of rapidly deteriorating hypertension and renal function. She had noticed Raynaud’s phenomenon since winter 2000 and swelling of her fingers since winter 2006. From spring 2008, she had experienced dyspnea during exercise. In November 2009, she suddenly suffered from severe dyspnea. She was admitted to the emergency department of the nearby hospital and then referred to our hospital. On examination, prominent edema and skin thickening spread all over the extremities. Her autoantibody screen revealed a positive anti-nuclear antibody with a titer of 1:320 homogeneous and speckled pattern, corresponding to anti-topoisomerase I antibody. Antineutrophil cytoplasmic antibodies and rheumatoid factor were negative. Complement levels and hepatic profiles were within normal limits, but her renal profile revealed markedly elevated serum creatinine level (7.72 mg/dL). Erythrocyte sedimentation rate (114 mm/h) and C-reactive protein (2.22 mg/dL) were elevated. A skin biopsy from the right forearm showed diffuse dermal fibrosis and a slight lymphocytic perivascular infiltrate. High-resolution computed tomography (HRCT) scan of the lungs revealed early bibasilar interstitial changes (Fig. 1a). A diagnosis of SSc with ongoing renal crisis was made, and enalapril and nicardipine were introduced. However,
the renal dysfunction was progressive and HD was introduced. After that, the patient became stable and was discharged.

In July 2010, she became increasingly dyspneic and the dry cough worsened. A blood test revealed increasing KL-6 and SP-D values (Fig. 2). The patient was clinically quite unwell with evidence of progressive worsening of ILD. Under close communication with nephrologists, we decided to treat this patient with IVCY to halt the deterioration. Before the therapy, she had been treated with HD for 3 h, three times a week. At the introduction of the therapy, the patient was admitted and the schedule was changed to HD twice a week (Tuesday and Friday) because the pre-dialysis serum creatinine had been improving. An intermediate dose of prednisone (20 mg/day) was started and the first IVCY was infused on Wednesday, the day after the HD, to avoid the clearance of cyclophosphamide by HD. Considering the potential increased risk for adverse events due to prolonged drug exposure caused by decreased clearance, the initial dose of 370 mg, a half dose of 500 mg/m² body surface area commonly administrated, was given without hydration infusion, which is routinely done for IVCY against SSc-ILD at our facility to prevent interstitial cystitis. Thus, the patient was started on a regime of monthly infusions with a half dose of IVCY for 5 months.

There was a good response to induction therapy with IVCY and no remarkable adverse event was noticed. The patient felt clinically better and did not complain of dyspnea or dry cough after the first two pulses. A HRCT scan of the lungs done in October 2010, post-induction of remission therapy with IVCY, revealed significant improvement of ILD (Fig. 1b). Even though the pulmonary function test results did not show similar improvements, the patient was symptomatically (i.e. dyspnea and dry cough) quite well. Markers of interstitial lung disease, KL-6 and SP-D, kept increasing during the first three pulses, but SP-D started to decline after the third pulse, followed by the decrease in KL-6 value (Fig. 2). The HRCT lung scans done in January 2011 revealed minimal early bibasilar interstitial and bronchiectatic changes (data not shown). There was no evidence of progression of fibrosis or ground glass appearance to suggest active ILD. We seemed to have been successful in preventing further progression of ILD without any significant adverse event. All clinical and biochemical parameters were normal. The patient is undergoing regular reviews to watch out for relapse of ILD or worsening of systemic symptoms.

DISCUSSION

Intravenous cyclophosphamide pulse is an established treatment for various autoimmune inflammatory diseases, including systemic lupus erythematosus (SLE) and systemic vasculitis. Given that patients with SLE and systemic vasculitis, such as
granulomatosis with polyangiitis and microscopic polyangiitis, often manifest renal insufficiency and terminal renal failure, it is not rare to administrate IVCY to patients with reduced renal function and on HD. In case of SSc, however, there has been no report regarding the administration of IVCY to patients with ILD under HD although the combination therapy of prednisone and IVCY is the first-line treatment against SSc-ILD, in which SRC occasionally coexists.

The important factor determining the efficacy and toxicity of IVCY is the concentration of its effective metabolite, phosphoramidemustard, which has the most ultimate alkylating property.9,10 Prednisone potentially reduces the terminal elimination half-life and increases the biotransformation rate of cyclophosphamide,9 which is a theoretical reason why the combination therapy of IVCY with prednisone is recommended to obtain its maximal clinical efficacy. As for the impact of reduced renal function on the pharmacokinetics and toxicity profile of cyclophosphamide, it is still controversial whether or not dose adjustment is recommended. Some studies showed no influence of renal dysfunction on the pharmacokinetics and toxicity of cyclophosphamide,9–12 while others reported the decrease in clearance of both cyclophosphamide and its alkylation metabolites resulting in an enhanced toxicity.10–12 Following these studies and others reporting the pharmacokinetics of cyclophosphamide in patients on HD,13,14 Haubitz et al.15 demonstrated the detailed data regarding the impact of HD on the pharmacokinetics of cyclophosphamide in 15 patients with autoimmune diseases treated with IVCY. According to their results, the clearance of cyclophosphamide is decreased in patients with reduced renal function, thereby resulting in an increased systemic drug exposure. Furthermore, cyclophosphamide is effectively eliminated from systemic circulation by HD, while the area under the curve of cyclophosphamide is almost identical to that of healthy controls when 3-h HD is carried out 7 h after the administration of IVCY. Based on these data, the authors concluded that dose reduction of 20–30%, depending on the degree of renal insufficiency, is suggested to prevent potential therapy-related toxicity and that dialysis should not be initiated earlier than 12 h after IVCY, which would prevent drug removal in the early distribution phase but would still correct for the prolonged terminal elimination phase.15

In our case, based on the previous data, we decided to administrate a half dose of IVCY to carefully avoid the potential toxicity while conducting HD 48 h after the administration in order to obtain its maximal clinical effect on SSc-ILD. Given that circulating cyclophosphamide concentration is decreased below the biologically active levels 24 h after the administration,15 it was assumed that HD did not weaken the effect of IVCY in the present case. In spite of the modest dose, her subjective symptoms significantly improved together with the marked decrease in ground glass opacity on pulmonary HRCT images, while we failed to detect any clinical and laboratory adverse event throughout the course of whole IVCY.

In summary, we herein reported the first case of SSc-ILD on HD who was treated effectively and safely with IVCY. Although the optimal dose of cyclophosphamide and the timing of HD have to be considered carefully in each case, we need to be aware that early intervention with IVCY is helpful in induction of remission in SSc-ILD even if on HD.

CONFLICT OF INTEREST: None.

REFERENCES