Once-daily oral administration of cyclosporine in a lung transplant patient with a history of renal toxicity of calcineurin inhibitors

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Abstract

Cyclosporine is usually administered orally in two divided doses every 12 h in transplant patients. However, some patients have difficulty in achieving therapeutic levels after transplantation. In fact, cyclosporine is reportedly administered once daily in renal and liver transplantation cases, but not in lung transplantation cases. We report a patient with a history of calcineurin inhibitor-induced renal toxicity who successfully underwent living-donor lobar lung transplantation (LDLLT) with the novel immunosuppressive strategy of once-daily administration of cyclosporine. An 18-year-old man with progressive respiratory insufficiency after bone marrow transplantation was referred to our hospital for lung transplantation. He had a history of renal toxicity due to calcineurin inhibitors. Based on his history of tacrolimus- and cyclosporine-induced renal toxicity, we decided to initiate basiliximab as induction therapy, followed by once-daily cyclosporine administration to obtain high enough blood cyclosporine concentrations at 2 h post-dose (C2) and lowered trough blood concentrations (C0) for protection of renal function as maintenance therapy. LDLLT was successfully performed, and the postoperative course was uneventful and free of rejection episodes. Cyclosporine dosing was adjusted with intensive therapeutic drug monitoring of blood cyclosporine levels. One year after LDLLT, the patient is alive and well with no problems with daily life activities.

Keywords: Calcineurin inhibitor • Induction therapy • Lung transplantation • Renal toxicity

INTRODUCTION

Cyclosporine is a calcineurin inhibitor that has been widely used to prevent rejections after transplantation. Cyclosporine has a narrow therapeutic range and shows large inter- and intraindividual pharmacokinetic variability. It has been shown that the area under the concentration-time curve (AUC) is a better reflection of total exposure to cyclosporine and its immunosuppressive activity for each individual patient. Therefore, AUC monitoring is emphasized as an ideal way for optimizing the dose of cyclosporine [1–4]. However, routine monitoring of cyclosporine AUC is an impractical strategy to require multiple blood sampling. Therefore, therapeutic drug monitoring of trough blood concentrations (C0) is required to prevent adverse effects such as nephrotoxicity. Furthermore, blood cyclosporine concentrations at 2 h post-dose (C2) have been shown to be a good predictor of the absorption profile [1]. Cyclosporine is usually administered orally in two divided doses every 12 h in transplant patients, but some patients have difficulty in achieving therapeutic levels after transplantation because of prolonged and/or delayed absorption [2]. Moreover, C0 levels are frequently elevated by a continuous dose escalation. In such cases, a single daily administration of the equivalent cumulative dose of cyclosporine may provide an alternative strategy to the use of intravenous cyclosporine, in terms of lowering C0 levels and ensuring adequate C2 levels [3]. In fact, cyclosporine is reportedly administered once daily in renal and liver transplantation cases [2, 4], but not in lung transplantation cases. We report a patient with a history of calcineurin inhibitor-induced renal toxicity who successfully underwent living-donor lobar lung transplantation (LDLLT) with the novel immunosuppressive strategy of once-daily administration of cyclosporine.

CASE REPORT

An 18-year-old man with progressive respiratory insufficiency was referred to our hospital for lung transplantation. At Age 12, he developed aplastic anaemia and was treated with immunosuppressive therapy, but developed renal toxicity caused by cyclosporine treatment with a target trough level (C0) of 140–170 ng/ml. At Age 13, the patient underwent bone marrow transplantation from his sister. Tacrolimus was used for immunosuppression, which was terminated after 2 months of treatment because the patient developed renal toxicity. Renal biopsy revealed tacrolimus-induced nephrotoxicity. The patient then developed progressive bronchiolitis obliterans as a result of graft versus host disease. At the time of referral, he was nearly bedridden and his height was 160 cm with a body weight of 38 kg. After repeated informed consent, we decided to perform LDLLT using his father’s right lower lobe and his brother’s left lower lobe. The preoperative
serum creatinine level was 0.8 mg/dl, but 24 h creatinine clearance was 50 ml/min. Urine dipstick test results were positive for both protein and blood (3+). Development of renal dysfunction was highly probable with the usual postoperative immunosuppressive therapy. Based on his history of tacrolimus- and cyclosporine-induced renal toxicity, we decided to initiate basiliximab as induction therapy, followed by once-daily cyclosporine administration to obtain high enough C2 level and lowered C0 level of cyclosporine for protection of renal function as maintenance therapy. LDLT was successfully performed, and the post-operative course was uneventful and free of rejection episodes. The patient was discharged 57 days after LDLT. Cyclosporine dosing was adjusted with intensive therapeutic drug monitoring of blood cyclosporine levels (Fig. 1). AUC between 0 and 12 h after dose administration of cyclosporine [AUC (0–12)] was evaluated at 4 days and 2 weeks after LDLT (2773 vs 11 689 ng h ml$^{-1}$). In addition, AUC during 4 h after dose administration [AUC (0–4)] was 1621 and 5203 ng h ml$^{-1}$, respectively. One year after LDLT, the patient is alive and well with no problems with daily life activities. Blood cyclosporine concentration is stable over long periods and AUC (0–4) was 2949 ng h ml$^{-1}$ at 1 year after LDLT.

**DISCUSSION**

Despite medical advances in the field of haematopoietic stem cell transplantation (HSCT), progressive and irreversible pulmonary complications after HSCT remain significant and leading causes of death. Lung transplantation is one of the last options for such patients, but it has been considered a challenging procedure because general condition of such patients is relatively poor preoperatively and additional immunosuppression is required after lung transplantation [5]. In the current case, only small amount of prednisone had been administered preoperatively, but the patient was very thin with a body mass index of 14.8 kg/m$^2$ and always on the bed.

Once-daily oral administration of cyclosporine has been recommended, since it might effectively help achieve therapeutic peak blood concentrations without elevating trough levels [4]. Patients undergoing lung transplantation after HSCT often have preoperative extrapulmonary comorbidities, such as poor absorption and renal insufficiency [5]. In our patient, previous cyclosporine nephrotoxicity occurred even when C0 was relatively low. Therefore, based on the AUC (0–12) data, the target C0 level was set at 100–150 ng/ml during the first month after LDLT. In this setting, blood cyclosporine concentration at 2 h post-dose (C2) was relatively high at $\sim$1000 ng/ml. This implied that C2 had become higher than expected in the previous cyclosporine administration, which might result in nephrotoxicity. At 1 month after LDLT, the target C0 level of cyclosporine was set about 100 ng/ml. As a result, the renal function of the patient was protected from further dysfunction. Simultaneously, it was observed that there was no immunological reaction including rejection, and therefore, the blood concentration of cyclosporine was suggested to be enough to the present patient against immunological reaction. The present case suggests that a once-daily oral administration

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**Figure 1:** (A) Blood cyclosporine concentration at 2 h post-dose (C2). The target C2 was set at 800–1000 ng/ml. (B) Blood cyclosporine concentration before dosing (C0) and daily oral dose after living-donor lobar lung transplantation (LDLLT). Cyclosporine dosing was adjusted with intensive therapeutic drug monitoring of blood cyclosporine levels. The target C0 was set at 100–150 ng/ml during the first month after LDLLT. At 1 month after LDLLT, the target C0 level of cyclosporine was set around 100 ng/ml. (C) Serum creatinine level and urine dipstick data (urine protein and blood) in the perioperative period.
of cyclosporine may be a novel and convenient strategy for patients with renal dysfunction.

In lung transplantation, basiliximab has been practically used for patients with renal insufficiency as a temporary alternative to calcineurin inhibitors. In thoracic transplantation, basiliximab has been used for patients with renal insufficiency as an induction therapy. In this case, we used basiliximab to deliberately introduce cyclosporine to the patient with a history of renal toxicity from calcineurin inhibitors.

Since recipients often receive organs from parents and siblings in LDLLT, those organs must have various immunological advantages in comparison with organs in the cadaveric lung transplantation. In the future, a trial in a group of standard cadaveric lung transplantation with a longer follow-up should be conducted to verify the outcomes including the risk of incidence of bronchiolitis obliterans syndrome.

In conclusion, we successfully conducted LDLLT in a patient with a history of renal toxicity of calcineurin inhibitors by the novel immunosuppressive strategy of once-daily administration of cyclosporine.

Conflict of interest: none declared.

REFERENCES