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CASE REPORT

Severe Anaphylaxis During Allogeneic Hematopoietic Stem Cell Transplantation in a Patient with Aplastic Anemia: Case Report of Individualized Pharmaceutical Care and Literature Review

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SUMMARY

Background: **Cyclosporine injection is usually applied in allogeneic hematopoietic stem cell transplantation (Allo-HSCT) during induction phase. Anaphylaxis to cyclosporine injection is rare and how to deal with this issue in clinical practice is intractable.**
Methods: **We report a Chinese male patient with aplastic anemia who underwent allogeneic bone marrow transplantation (BMT) from his brother where HLA totally matched (10/10). Cyclosporine at a dose of 3 mg/kg was started by continuous infusion over 24 hours on day -1 of BMT and the patient showed sever anaphylaxis symptoms. He was then given oral capsules of cyclosporine (Sandimmun) at a conversion ratio 2:1. No further anaphylactic reaction was observed. The BM cells were successfully engrafted without causing severe GVHD. Moreover, frequent TDM monitoring as well as CYP3A4/CYP3A5/MDR1 genotyping were given so as to tailor the oral dosage of cyclosporine individually and prevent the adverse reaction between cyclosporine and posaconazole.**
Results: **The patient carried CYP3A5*3 GG genotype and the concentration of cyclosporine remained steady in the period of conversion and combination of cyclosporine and posaconazole. Consequently, the patient reported no allergy after conversion to oral cyclosporine.**
Conclusions: **Polyoxyethylated castor oil that is contained in cyclosporine may be the main allergen. Changing to oral capsules that do not contain this medicinal excipient instead of cyclosporine injection would no longer cause an allergic reaction. Rational use of immunosuppressants and prophylaxis antibiotics may need close cooperation between physicians and pharmacists to avoid side effects and harmful interactions.**
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KEY WORDS

anaphylaxis, allogeneic hematopoietic stem cell transplantation, individualized pharmaceutical care

INTRODUCTION

Allogeneic hematopoietic stem cell transplantation is a cure for severe aplastic anemia. Cyclosporine is a key agent which is approved for the prevention of graft versus-host disease (GVHD) as well as to allow engraftment of transplanted organs including kidney, liver, and heart allografts [1,2]. Anaphylaxis is a rare complica-

tion of intravenous cyclosporine. However, some individuals were reported to be allergic to intravenous cyclosporine [2,3]. In that case, how to adjust the treatment regimen becomes an intractable problem, especially for those patients had undergone allo-HSCT.

Cyclosporine is a potent immunosuppressant widely used to block the transcription of cytokine genes in activated T cells [4]. Although tacrolimus could be prescribed as a substitute for cyclosporine in unrelated-donor transplantation, castor oil is also contained in the formulation.

CASE REPORT

A 21-year-old male patient with severe aplastic anemia, was admitted for allogeneic bone marrow transplantation with an HLA identical sibling donor. He had a medical history of blood transfusion. Conditioning regimen with cyclophosphamide and ATG were initiated for 4 days and intravenous cyclosporine (Sandimmun, Novartis, Basel, Switzerland) was started 5 days before allogeneic bone marrow transplantation at a dose of 70 mg over a 24-hour continuous infusion. He began to complain of chest tightness, dizziness, nausea. His vital signs were as follows: purple lips, blood pressure 70/50 mmHg; pulse rate, 100/minute; heart rate 96/minute; and body temperature, 36.7°C. Administration of cyclosporine was immediately stopped. He then received systemic corticosteroid (Methylprednisolone, 40 mg). His complaints resolved after treatment.

Because alternative treatment was needed for GVHD prevention in this patient, oral capsules of cyclosporine (Sandimmun Neoral, Novartis) that did not contain the causative polyoxyethylated castor oils, Cremophor EL and Cremophor RH 60, were administered. Oral cyclosporine (Sandimmun Neoral) did not cause a significant reaction and was administered 150 mg twice daily. The patient received bone marrow mononuclear cells that had been harvested from his brother with successful engraftment. We achieved dosage adjustment by monitoring cyclosporine blood levels. The patient was discharged without acute GVHD on day 30 and was taking 100 mg cyclosporine twice daily.

DISCUSSION

Anaphylaxis

Anaphylaxis to intravenous cyclosporine was first described in a renal transplant recipient in whom hypotension and dyspnea developed immediately after the start of intravenous cyclosporine and disappeared within 30 minutes after discontinuation of the infusion [5]. Anaphylaxis was fatal in a patient who received intravenous cyclosporine for liver transplantation which resulted in cardiopulmonary arrest [6]. Polyoxyethylated castor oil, a solubilizer used in the injection formulation of cyclosporine, is thought to be responsible for the anaphylaxis, because similar anaphylactic reactions have been observed after treatment with other drugs containing polyoxyethylated castor oil, such as paclitaxel, multivitamin hydrosol, and vitamin K [7-9]. Anaphylaxis to intravenous cyclosporine was also reported in patients who underwent allo-HSCT [2,3].

Polyoxyethylated castor oil is a nonionic solubilizer and emulsifier prepared by reacting varying amounts of ethylene oxide with either castor oil or hydrogenated castor oil. The Cremophor series (Cremophor EL, Cremophor RH 40, Cremophor RH 60, etc.) are well-known among several available materials [10]. Polyoxyethylated castor oil is particularly useful as a vehicle for a variety of hydrophobic drugs. Because of its properties, polyoxyethylated castor oil has been widely used to improve the solubility of water-insoluble drugs such as anticancer, immunosuppressive, analgesic, anesthetic drugs, vitamins, and new synthetic water-insoluble compounds. In fact, pre-conditioning therapy may be provided as an effective means to prevent anaphylaxis. The drug instructions for paclitaxel injection recommended premedication of orally taken dexamethasone 20 mg 12 hours and 6 hours before paclitaxel injection administration, and intravenous infusion of 50 mg diphenhydramine and 300 mg cimetidine or 50 mg ranitidine 30 - 60 minutes before paclitaxel injection administration. Premedication before paclitaxel injection were reported to reduce the mortality from anaphylactic reactions with paclitaxel [11].

Conversion ratio

For those with serious hypersensitivity reactions caused by intravenous tacrolimus and cyclosporine, it is important to know what the alternatives could be. Formulations that do not contain castor oil derivatives appear to be a safe alternative. Oral formulations are available as a capsule. However, the conversion ratio between infusion to oral cyclosporine becomes another problem. Although guidelines and literatures recommend the dose conversion ratio of 1:2 to be appropriate, there are differences between individuals. Different from the intravenous formulation, oral cyclosporine should be absorbed mainly through intestinal mucosa cells by P-glycoprotein (P-gp) and metabolized by CYP3A4/ CYP3A5. Single nucleotide polymorphism of CYP3A4/ CYP3A5 may contribute to interpatient variations of cyclosporine capsule absorption. Additionally, highly variable interpatient pharmacokinetics have been observed regarding oral administration due to differences in gastrointestinal conditions, gastrointestinal inflammation due to either mucositis or GVHD resulting in a higher AUC [12]. Yasuyuki investigated the pharmacokinetics of cyclosporine when converting from twice-daily infusion to oral administration in 11 Allo-HSCT patients. The results showed the bioavailability of oral cyclosporine ranged from 0.41 to 0.94 (0.58 ± 0.15), which suggested broad variations among individuals when taking orally [13].

Table 1. Drug Chart Review and potent interaction screened.

Drug	Strength	Frequency	Start	End
Cyclosporine injection	70 mg	Q12H	2018.6.29	2018.6.29
Cyclosporine soft capsule	150 mg	Q12H	2018.7.5	2018.7.17
Cyclosporine soft capsule	125 mg	Q12H	2018.7.17	2018.8.1
Cyclosporine soft capsule	100 mg	Q12H	2018.8.2	
Mycophenolate mofetil capsules	500 mg	BID	2018.7.6	
Posaconazole oral solution	5 mL	TID	2018.7.7	2018.8.4

Table 2. Genotyping for CYP3A5*3.

CYP3A5*3 (G>A)	GG	Homozygous mutation

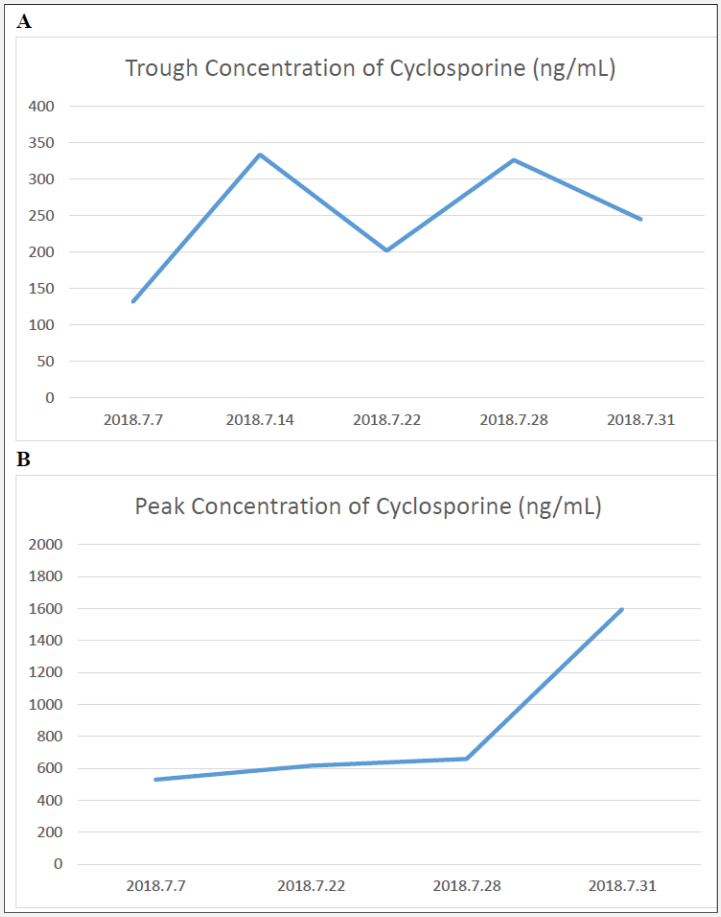

Figure 1. Therapeutic Monitoring for Cyclosporine.

A - Trough concentration of cyclosporine (ng/mL). B - Peak concentration of cyclosporine (ng/mL).

TDM and pharmaceutical care

As the patient underwent anaphylaxis to cyclosporine injection, we recommend the physicians to prescribe a genotype of CYP3A5*3, which is the main metabolized CYP450 enzyme. The results indicate the patient was a CYP3A5*3 homozygous mutation carrier, which suggest the dosage of cyclosporine should be reduced to 70% - 75% [14-15]. Additionally, pharmacists screened all the drugs the patient used and found posaconazole may have potent drug-to-drug interaction with cyclosporine. According to US National Formulary, cyclosporine dosage should be reduced to approximately 75% of the ideal dose. Combining the factors of simultaneous use of posaconazole and CYP3A5*3 mutation, the dosage of cyclosporine should be reduced to approximately 60%. In terms of this patient, we assisted physicians in adjusting the dosage of cyclosporine tablets to 100 mg q12h according to the TDM and genotype results (Table 1 - 2). It has been reported that AUC0-24 higher than 10,000 ng.h/mL were reported to prevent severe GVHD [13], the mean C2h of which is above 1,000 ng/mL. The concentration of cyclosporine in this patient was then steady and reached a desired C2h concentration and no severe GVHD was observed. Under the careful medical care, the patient was discharged without any side effects.

CONCLUSION

Multidiscipline collaboration and individualized pharmaceutical care play a vital role during the Allo-HSCT process. Intensive and individualized pharmaceutical care may provide practical solutions in clinical, especially in special circumstances.

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Declaration of Interest:

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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