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ORIGINAL ARTICLE

Retrospective Study

Higher plasma bilirubin predicts veno-occlusive disease in early childhood undergoing hematopoietic stem cell transplantation with cyclosporine

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Abstract

AIM: To analyze the association between plasma bilirubin levels and veno-occlusive disease (VOD) in non-adult patients undergoing hematopoietic stem cell transplantation (HSCT) during cyclosporine therapy.

METHODS: A total of 123 patients taking cyclosporine

were evaluated using an electronic medical system at the Seoul National University Children's Hospital from the years 2004 through 2011. Patients were grouped by age and analyzed for incidence and type of adverse drug reactions (ADRs) including VOD.

RESULTS: The HSCT patients were divided into three age groups: G#1 $\geqslant$ 18; 9 $\leqslant$ G#2 $\leqslant$ 17; and G#3 $\leqslant$ 8 years of age). The majority of transplant donor types were cord blood transplantations. Most prevalent ADRs represented acute graft-*vs*-host disease (aGVHD) and VOD. Although the incidences of aGVHD did not vary among the groups, the higher frequency ratios of VOD in G#3 suggested that an age of 8 or younger is a risk factor for developing VOD in HSCT patients. After cyclosporine therapy, the trough plasma concentrations of cyclosporine were lower in G#3 than in G#1, indicative of its increased clearance. Moreover, in G#3 only, a maximal total bilirubin level (BILmax) of $\geqslant$ 1.4 mg/dL correlated with VOD incidence after cyclosporine therapy.

CONCLUSION: HSCT patients 8 years of age or younger are more at risk for developing VOD, diagnosed as hyperbilirubinemia, tender hepatomegaly, and ascites/weight gain after cyclosporine therapy, which may be represented by a criterion of plasma BILmax being $\geqslant$ 1.4 mg/dL, suggestive of more sensitive VOD indication in this age group.

Key words: Hematopoietic stem cell transplantation; Veno-occlusive disease; Cyclosporine; Adverse drug reaction; Total bilirubin

Core tip: This study analyzed the association between plasma bilirubin and veno-occlusive disease (VOD) in childhood undergoing hematopoietic stem cell transplantation (HSCT) during cyclosporine therapy. Here, we report that age of 8 or under may be a risk factor for VOD in CsA-treated patients who underwent HSCT with differential clearance of CsA. Another finding is that a criterion of 1.4 mg/dL of plasma maximal total bilirubin level or higher content alone closely represents the incidence of VOD in early childhood patients with HSCT in CsA therapy. Information shown in this study would be of great help to understand VOD occurring during CsA medication and to find optimal pharmacotherapy in HSCT patients.

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INTRODUCTION

Cyclosporine is a major immunosuppressant for organ transplantation, and is widely used for the prophylactic treatment of acute graft-*vs*-host disease (aGVHD) after hematopoietic stem cell transplantation (HSCT)[1]. However, the morbidity and mortality resulting from acute, or subsequently following chronic GVHD, and veno-occlusive disease (VOD), as indicated by hyperbilirubinemia, tender hepatomegaly, and ascites, are obstacles to the use of cyclosporine alone or in combination with other agents[2]. Clinical studies on cyclosporine therapy demonstrated differences between neonate, child and adult populations in the incidence of adverse drug reactions (ADRs)[3]. Since these events are closely linked to the metabolic burden and/or clearance of the drug, ADRs should be monitored and avoided depending on the types of transplantation, age groups and pharmacokinetic profiles. In particular, the dose regimens and therapeutic concentrations need to be appropriately adjusted for optimal efficacy and/or minimized ADRs.

Cyclosporine therapy should be carefully monitored as a therapeutic drug monitoring system[4]. Monitoring of pharmacokinetic profiles, including oral bioavailability, has been claimed in the context of successful pharmacotherapy because intestinal absorption of cyclosporine varies depending on the type of transplantation, age, and other parameters of patients[5-9]. In general, patients of a young age seem to be more at risk for ADRs to cyclosporine, and exhibit different ADR profiles[10]. Therefore, the oral dose of cyclosporine required for the maintenance of therapeutic blood levels is significantly augmented in childhood patients[5]. In addition to the narrow therapeutic range of cyclosporine, the types and incidences of cyclosporine-induced ADRs vary depending on the types and severities of diseases, as well as patient age[11].

It has been recognized that wide variations exist in the plasma concentrations of cyclosporine among HSCT patients[12]. A limited number of studies have been performed in cyclosporine-treated neonates and children who underwent HSCT in the context of ADR monitoring[13]. In Seoul National University Hospital, the administered dose of cyclosporine was equally determined by the post-surgical day of HSCT, which frequently resulted in cyclosporine plasma concentrations being out of therapeutic range (150-250 ng/mL). Although the normalized doses of cyclosporine for transplant patients of childhood age were usually higher than those for adults, the plasma concentrations were significantly lower[3]. This raised the contention that biotransformation and/or excretion of cyclosporine is accelerated in childhood patients, which may be linked to ADRs, such as GVHD, nephrotoxicity, and neurotoxicity[13].

Age-different effects of cyclosporine therapy on the types and incidences of ADRs in HSCT patients are

Table 1 The characteristics of hematopoietic stem cell transplantation patients treated with cyclosporine (*n* = 123)

Characteristics	G#1 (*n* = 25)	G#2 (*n* = 70)	G#3 (*n* = 28)
Age (mean, SD)	20.3, 1.7	13.0, 2.5	5.8, 2.2
Initial body weight (mean, SD)	51.8, 11.1	37.8, 12.7	14.0, 4.0
Gender (M, %)	15 (60.0)	35 (50.0)	17 (60.7)
Liver function (mean, SD)			
ALT (mg/dL)	67.6, 95.8	67.1, 67.3	104, 133
AST (mg/dL)	70.2, 73.1	72.9, 61.5	161, 356
Doner types, *n* (%)			
Cord blood	15 (60.0)	41 (58.6)	21 (75.0)
Related donor	10 (40.0)	29 (41.4)	7 (25.0)
Types of disease, *n* (%)			
AA	5 (20.0)	6 (8.6)	1 (3.6)
ABL	4 (16.0)	5 (7.1)	2 (7.1)
ALL	10 (40.0)	28 (40.0)	7 (25.0)
AML	5 (20.0)	20 (28.6)	10 (35.7)
CML	0 (0.0)	2 (2.9)	0 (0.0)
JMML	0 (0.0)	0 (0.0)	4 (14.3)
MDS	1 (4.0)	2 (2.9)	1 (3.6)
Others	0 (0.0)	7 (10.0)	3 (10.7)
Observed events, *n* (%)			
aGVHD	13 (61.9)	26 (46.4)	13 (54.2)
cGVHD	1 (4.8)	4 (7.1)	0 (0.0)
VOD	2 (9.5)	13 (23.2)	7 (29.2)
DIC	4 (19.0)	4 (7.2)	2 (8.3)
Relapse	1 (4.8)	2 (3.6)	1 (4.2)
EF	0 (0.0)	7 (12.5)	1 (4.2)

Age groups: G#1, 18 years older; G#2, 9 to 17 years old; G#3, 8 years old or under. AA: Aplastic anemia; ABL: Acute biphenotypic leukemia; ALL: Acute lymphocytic leukemia; AML: Acute myelocytic leukemia; CML: Chronic myelocytic leukemia; JMML: Juvenile myelomonocytic leukemia; MDS: Myelo dysplastic syndromes; aGVHD: Acute graft versus host disease; cGVHD: Chronic graft versus host disease; VOD: Veno-occlusive disease; DIC: Disseminated intravascular coagulation; EF: Engraft failure; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase.

known[14-16]. Nevertheless, more sensitive indicator(s) would be of great help to avoid or minimize serious ADRs and to accomplish successful pharmacotherapy, especially in patients of the childhood population who would be more prone to drug-induced harmful effects. This study analyzed the association between plasma bilirubin levels and VOD in non-adult patients undergoing HSCT during cyclosporine therapy. Here, we report that marginally high levels of total plasma bilirubin reliably indicate VOD during cyclosporine therapy in the HSCT patient of early childhood.

MATERIALS AND METHODS

Datasets

This study was approved by the Institutional Review Board of Seoul National University Hospital (SNUH; H-1112-087-390, 2012.3.17), a 1961-bed medical center, on March 17, 2012. The data collected had anonymous codes representing patient files comprising the following medical information: Age, gender, medical diagnosis codes, date of HSCT, absolute neutrophil count, post-transplantation day, donor types (cord blood and related donor), body weight, body surface area, body temperature, types of ADRs, peak and trough concentrations of cyclosporine, serum hematocrit, alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum total bilirubin levels, dates of labs drawn, medications (generic and brand name, prescription date), and duration of chemotherapeutic agent along with co-prescribed drugs.

Patients

The database contained records of 123 patients (ages ranging from 2 to 24 with 68 males and 55 females) who had been hospitalized in SNUH from September 15, 2004 to December 31, 2012 and had undergone measurements of plasma cyclosporine levels using a radioimmunoassay kit. Cyclosporine concentrations were monitored on day 1, 4, 11 18, 24 and 28 after HSCT and at intervals of three or seven days after day 28 of HSCT in SNUH. Laboratory data were obtained from 123 patients, with three of them having HSCTs twice in this period. The total number of cyclosporine measurements was 2149, with an average of 17.5 measurements per patient.

HSCT patients who had been administered cyclosporine were divided into three groups based on age: G#1, 18 years of age or older; G#2, between 9 and 17 years of age; and G#3, 8 years of age or under. The median ages in G#1, G#2, and G#3 were 20, 13 and 6, respectively. Each group was additionally split into four subgroups by the levels of a maximal total bilirubin level (BILmax) [*i.e.*, BILmax (-), lower than 1.4 mg/dL of total plasma bilirubin; and BILmax (+), 1.4 mg/dL of total plasma bilirubin or higher] and VOD incidence [*i.e.*, VOD (-), no existing VOD; and VOD (+), existing VOD].

Statistical analysis

The Fisher exact test was chosen to determine differences in the frequency of BILmax $\geqslant$ 1.4 mg/dL between VOD (-) and VOD (+) groups. Multivariate analysis was performed to find risk factors for drug therapy. Data represent the median (0.5-24.0 mg/dL). Results were considered statistically significant if the *P*-value was less than 0.05. Statistical analyses were conducted using the Duncan and Fisher's tests in SPSS Version 12.0 (SPSS Inc., Chicago, IL, United States).

RESULTS

The characteristics of HSCT patients treated with cyclosporine (*n* = 123) are summarized in Table 1. Of the patients examined, cord blood transplantation constituted the majority of the transplant donor type (G#1, 60.0%; G#2, 58.6%; and G#3, 75.0%). The most prevalent ADR event observed was aGVHD (G#1, 61.9%; G#2, 46.4%; and G#3, 54.2%), whereas the second most frequent ADR event was VOD (9.5%-29.2%). Although the incidences of aGVHD, diagnosed as cytopenia and delayed immune reconstitution, did not vary much between the groups, the frequency ratios of VOD were significantly higher in G#3. Thus, being 8 years of age or under at the time of transplantation

Table 2 Median trough plasma concentrations and doses of cyclosporine in hematopoietic stem cell transplantation patients

Contents		G#1 (n = 25)	G#2 (n = 70)	G#3 (n = 28)
iv	Trough plasma concentration[b] (ng/mL)	535.6 (264.0-1214.0)[a]	448.9 (184.5-1070.0)	333.1 (152.5-819.0)
	Dose (mg/kg)	5.8 (3.9-7.7)	6.1 (3.5-14.2)	6.0 (3.8-9.3)
PO	Trough plasma concentration[b] (ng/mL)	345.9 (166.0-686.5)	247.7 (40.0-496.5)	204.4 (33.0-302.5)
	Dose (mg/kg)[c]	8.2 (3.4-11.4)	8.2 (1.6-17.5)	10.6 (6.0-24.6)

[a]The values in parenthesis represent the minimum and maximum trough plasma concentrations of cyclosporine; [b]G#1 was significantly different from G#2 or G#3 using Duncan test; [c]G#3 was significantly different from G#1 or G#2 using Duncan test. *iv*: Intravenous administration; PO: Per Os, which means oral administration.

Table 3 Two by two analyses between maximal plasma bilirubin contents and veno-occlusive disease in hematopoietic stem cell transplantation patients

	G#1 (n = 25)		G#2 (n = 70)		G#3 (n = 28)	
	BILmax (-)	BILmax (+)	BILmax (-)	BILmax (+)	BILmax (-)	BILmax (+)
VOD (+)	0	2	4	9	0	7
VOD (-)	5	18	28	29	17	4
P-value	1.00		0.356		0.0001	

BILmax (+): 1.4 mg/dL or higher; BILmax (-): Lower than 1.4 mg/dL. Data were analyzed using Fisher's test program. BILmax: A maximal total bilirubin level; VOD: Veno-occlusive disease.

would be a possible risk factor for VOD in patients who underwent HSCT from cord blood donors. In types of diseases, acute lymphoblastic leukemia and acute myeloid leukemia highly occurs in all three groups of patients, but there was no significant difference of the disease incidence rate depending on the age. Also the liver functions (*i.e.*, ALT and AST activities) were comparable in all groups of patients.

After intravenous administration, the trough plasma concentrations of cyclosporine were significantly lower (83.8% and 62.2% in G#2 and G#3, respectively, *vs* G#1) in G#2 or G#3 than in G#1, although the injected dose of cyclosporine was normalized to the patient body weight (Table 2). The trough plasma concentrations of cyclosporine were approximately 40% lower in G#3 than in G#1, indicative of its accelerated clearance in G#3. The trough plasma cyclosporine levels were similarly changed in the groups examined after oral administration; in this case, the oral dose was approximately 30% greater in G#3 than in G#1 (or G#2), suggesting the possibility that the bioavailability of cyclosporine was significantly lower in G#3 (Table 2). These results indicate that the clearance and/or turnover rate of cyclosporine in plasma might be augmented in G#3, whereas the oral bioavailability was lower in this group, implying the potential of increased detoxifying burden in the patients presumably due to accelerated biotransformation and excretion of cyclosporine.

Given the distinct difference in plasma cyclosporine concentrations and the potential of increased cyclosporine clearance in G#3, we next asked whether the incidences of VOD statistically correlated with total bilirubin levels in plasma among the patients examined. Setting the BILmax cutoff level at 2.0 mg/dL demonstrated an obvious increment in VOD incidences in high BILmax groups when G#2, G#3 or the total population was analyzed, although it failed in demonstrating increased VOD incidences when G#1 was solely analyzed (data not shown). More importantly, setting the BILmax cutoff level at 1.4 mg/dL (a minimal significant value obtained empirically) revealed an augmented incidence of VOD in the high BILmax group in G#3 ($P < 0.0001$), but not in G#1 or G#2, as determined by two-by-two analyses (Table 3).

DISCUSSION

ADR-related admissions are a problem with a high prevalence[17,18]. Pérez Menéndez-Conde *et al*[18] reported that 19.4% of admissions were direct consequences of ADRs, 65% of which were preventable[19]. In particular, cyclosporine therapy causes various ADRs (*e.g.*, 20% of infectious complications during the therapy and 5% of severe GVHD)[20,21], with approximately 6% of admissions eliciting permanent damage, including seizures or death[22]. In general, the dose of cyclosporine is calculated for transplant patients primarily on the basis of body weight[23]. However, this approach has limitations, such as the development of aGVHD, cGVHD, hepatotoxicity, gastrointestinal disorders, infections and hemorrhagic cystitis[24]. Large variations in plasma cyclosporine concentrations exist in individuals (*i.e.*, 5-8 fold differences)[25]. Since the biotransformation capacities of endogenous and exogenous substances vary depending on the stage of development and maturation, attention should be directed to cyclosporine clearance. The results of this study demonstrated the impact of age differences on the incidence and type of ADRs during cyclosporine therapy in HSCT patients of early childhood as compared to adolescent patients.

A major advantage of HSCT is the potential for therapeutic benefits from graft-*vs*-leukemia effects, which are mediated by donor T and natural killer cells[26]. Unfortunately, graft-*vs*-leukemia effects are closely linked to aGVHD as the major limiting toxicity of allogeneic transplantation, which causes damage to the skin, gastrointestinal tract, and liver[27]. Studies have shown that aGVHD frequently occurred when plasma concentrations of cyclosporine decreased to 125-200 ng/mL 12 h after treatment[25,28]. Depletion of T cells from the graft effectively prevented aGVHD, but it also limited graft-*vs*-leukemia effects, possibly increasing the rate of graft failure[29]. Therefore, plasma concentrations of immunosuppressant are currently one of the critical factors to maintain the proper balance between aGVHD and graft-*vs*-leukemia effects. The lowest plasma cyclosporine concentration (< 200 ng/mL) in the third week after transplantation showed a high risk factor related to aGVHD (grades Ⅱ-Ⅳ) in HSCT patients[30]. Thus, assessment of cyclosporine levels is a valuable diagnostic tool to predict aGVHD. In the present study, we observed that the incidences of aGVHD (*i.e.*, cytopenia and delayed immune reconstitution) were not much different among the groups examined, which supports the appropriateness of the pharmacotherapy.

Patients currently meet McDonald's VOD-Seattle Criteria by exhibiting two or more of the following criteria: Hyperbilirubinemia > 2 mg/dL, tender hepatomegaly, and either ascites or weight gain (> 2%). A key finding of this study is that VOD occurrences were significantly higher in G#3. Similarly, the incidences of VOD increased in childhood age[31], whereas VOD was frequently observed day 18 (the median) after intravenous administration of cyclosporine[32]. When we compared the plasma levels of cyclosporine and other pharmacokinetic parameters, the turnover rate of cyclosporine seemed to vary in different age groups. Our finding showing lower plasma cyclosporine level with higher occurrence of VOD in G#3 differs from the previous report that high plasma concentrations or high doses of drugs in pediatric HSCT patients related to the frequent and severe VOD in different therapy in HSCT patients[33]. VOD occurrence seems to be associated with clearance of endogenous compounds as well as cyclosporine[34]. It has also been suggested that the clearance rate of cyclosporine may affect VOD and total bilirubin levels in blood[34]. This idea is consistent with the finding that the pharmacokinetic profile of cyclosporine was characterized by substantially faster elimination in children compared to adults, which necessitated more frequent dosing intervals and higher doses for younger children[7,35]. So, low plasma cyclosporine levels in G#3 may reflect its high turnover rate. Overall, our results and others support the contention that the turnover rate of cyclosporine is increased, particularly in HSCT patients of early childhood.

Our finding that HSCT patients of 8 years of age or under were more at risk for the reactions of VOD, which was distinctively characterized by the plasma BILmax level being ⩾ 1.4 mg/dL, indicates that plasma BILmax alone may serve as a valuable marker of VOD in this particular patient population. Since a large fraction of cyclosporine binds with erythrocytes (41%-50%)[36], cyclosporine-induced hyperbilirubinemia may result from destabilization and/or disruption of red blood cell membranes, with the consequent release of heme for biodegradation and excretion. It has also been shown that the clearance of red blood cells was slower, whereas the maturity and differentiation of red blood cells were lower in children compared to other groups[37]. Disruption of canaliculi in children has also been shown to increase, even at lower cyclosporine concentrations[38]. Therefore, the frequency of splenomegaly increases presumably due to the clearance of damaged red blood cells and debris, along with heme disposal, resulting in the subsequent production of bilirubin[39]. Consistently, red blood cells may be impaired after cyclosporine therapy, especially during radiation therapy[40].

Since cyclosporine is mainly oxidized *via* cytochrome P450s 3A4 (CYP3A4), followed by glucuronide conjugation *via* UDP-glucuronosyltransferase 1A1 (UGT1A1) and UGT2B7, total bilirubin levels in the blood would increase, enhancing the burden of detoxification[41]. Cyclosporine is primarily metabolized by CYP3A4 in the liver, 95% of which is excreted *via* the biliary route. The main reason for the low bioavailability of cyclosporine may be due to its extensive intestinal metabolism by CYPs[42]. The various rate and extent of cyclosporine metabolism, depending on age and drug interactions (60%-90%), may be related with polymorphisms of CYP3A4[43]. The genetic associations between UGT variations and cyclosporine pharmacokinetics in patients would also affect its efficacy and ADRs (*e.g.*, GVHD, hepatic and/or gastrointestinal disorders) presumably due to unpredictable cyclosporine concentrations[44]. Our results showed that plasma cyclosporine levels were significantly lower in G#3 despite the highest normalized dose. Clearance of endogenous bilirubin might also be reduced in the patients presumably due to relatively low rate of metabolism. Thus, cyclosporine biotransformation may change depending on the metabolic clearance of bilirubin, which would increase in early childhood compared to adolescents and/or adults[45]. Alterations in red blood cell turnover and/or interference of biliary excretion of glucuronidated cyclosporine would also contribute to total plasma bilirubin levels[46].

The value of pharmacist-provided drug-monitoring care to transplant recipients has been recognized as a beneficial service[47]. Considering the complexity of pharmacotherapy, pharmacists need to implement clinically relevant interventions on the transplant unit[48]. Although the dangers of ADRs are well recognized by clinicians and pharmacists, the efforts to elucidate the basis of ADRs still exist in clinical fields[49]. This situation stimulated attempts to validate ways of ADR monitoring by developing new and critical indicators, algorithms and analytical tools[50,51]. HSCT patients represent a population at high risk for drug-related problems[52]. Our

results demonstrate that HSCT patients 8 years of age or under are at higher risk for developing the reactions of VOD after cyclosporine therapy, which may be indicated by plasma BILmax levels being ⩾ 1.4 mg/dL, suggesting that this new criterion alone may be used as an indicator of VOD during cyclosporine therapy in HSCT patients of young childhood. A guideline for ADR-related problems and interventions may aid staffs working in the HSCT unit to optimize pharmaceutical care of patients, thereby reducing economic costs resulting from inappropriate drug utilization.

COMMENTS

Background

The incidence of veno-occlusive disease (VOD) differs from the ages of childhood, which is an obstacle of the use of cyclosporine, immunosuppressant for organ transplantation. Especially, the VOD incidence was higher in cyclosporine-treated neonates and children who underwent hematopoietic stem cell transplantation (HSCT). Therefore, the authors analyzed the association between plasma bilirubin levels and VOD in childhood patients undergoing HSCT during cyclosporine therapy.

Research frontiers

The sensitive indicator(s) would be of great help to avoid or minimize serious VOD and to accomplish successful cyclosporine therapy, especially in patients of the childhood population with higher VOD incidence. The results of this study contribute to clarifying the associations of bilirubin, VOD and cyclosporine concentrations.

Innovations and breakthroughs

Although age-different effects of cyclosporine therapy on various adverse drug reactions in HSCT patients are existing, the association between plasma bilirubin levels and VOD in non-adult patients undergoing HSCT during cyclosporine therapy was not reported yet. Thus, the authors report that marginally high levels of total plasma bilirubin reliably indicate VOD during cyclosporine therapy in the HSCT patient of early childhood.

Applications

A plasma BILmax levels being ⩾ 1.4 mg/dL may be used as an indicator of VOD during cyclosporine therapy in HSCT patients of young childhood. A guideline for adverse drug reaction-related problems and interventions may aid staffs working in the HSCT unit to optimize pharmaceutical care of patients, thereby reducing economic costs resulting from inappropriate drug utilization.

Terminology

A maximal total bilirubin level (BILmax) (-): Lower than 1.4 mg/dL of total bilirubin during cyclosporine therapy; BILmax (+): 1.4 mg/dL of total plasma bilirubin or higher during cyclosporine therapy.

Peer-review

This review is well written, presenting a very significant issue of "an increased risk for developing VOD after cyclosporine treatments in younger (< 8 years old) generations". Authors also claimed that the plasma BILmax levels being ⩾ 1.4 mg/dL would provide a useful indicator to recognize the development of VOD in those generations.

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