# Cyclosporine Level at the Second Hour in Pediatric Hematopoietic Stem Cell Transplant Patients

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## Abstract

**In this retrospective study, cyclosporine levels at the second hour (C2 levels) were measured during oral cyclosporine intake in 28 pediatric hematopoietic stem cell transplant patients, and the relations between cyclosporine dosage and C0, C2 levels, C2/C0 ratio, and cyclosporine-related adverse effects were investigated.**

**Cyclosporine levels at the second hour levels were found to be significantly lower in children younger than 7 years old, suggesting age-related differences in absorption and metabolism of the drug. There were statistically significant correlations of both C0 and C2 levels with blood creatinine values. In addition, a statistically significant negative relation was found between C0 and C2 levels and serum potassium levels; this unexpected finding was attributed to multiple drug effects in the early posttransplant period. The common adverse effects of cyclosporine (gingival overgrowth, gynecomastia, and hypertrichosis) were also evaluated in this study, and no correlation was found between those adverse effects and C0, C2 levels, C2/C0 ratio, and cyclosporine dosage.**

**In the present study, despite the highly significant correlation of C2 levels with renal and metabolic effects, in pediatric hematopoietic stem cell transplant patients, measurement of C2 levels as a standard practice did not provide an advantage over C0 monitoring. However, the preliminary results suggest that C2 level monitoring could be useful in selected patients with increased risk of renal toxicity or in states where a better estimation of gastrointestinal absorption is needed.**

**Key words:** *Cyclosporine, Hematopoietic stem cell transplant, Children, Nephrotoxicity, Adverse effects*

## Introduction

Cyclosporine A is the most-common prophylactic immunosuppressive drug used to suppress organ transplant rejection and graft-versus-host disease.[1] Cyclosporine binds to cyclophilin of lymphocytes and results in calcineurin inhibition, which suppresses interleukin-2 (IL-2) levels and inhibits T-lymphocyte proliferation.[2] The therapeutic range of the drug is narrow. The desirable pharmacologic effect is obtained only within narrow ranges of concentration in the blood. On the other hand, excessive levels of cyclosporine also can lead to adverse effects such as nephrotoxicity, hepatotoxicity, neurotoxicity, hypertension, gingival overgrowth, hypertrichosis, gynecomastia, and dyslipidemia.[3,4] There is significant interindividual and intraindividual variability in the pharmacokinetics of the drug; therefore, monitoring the cyclosporine level is essential to optimize immunosuppressive therapy.[5] In solid organ transplant, the current practice of monitoring cyclosporine trough levels (C0) or 2 hours after the oral dosage (C2), or both, varies between centers. Cyclosporine levels during the second hour sampling are valuable in determining individual dosing, particularly in patients with poor or erratic drug absorption or in the early posttransplant period in organ transplants.[6] In the hematopoietic stem cell transplant setting, current practice involves trough-level monitoring, but the observation of frequent adverse effects and an unacceptably high rate of acute graft-versus-host disease suggest that alternative

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means of drug monitoring may be useful.[7] It has been demonstrated that cyclosporine oral absorption may be influenced by intestinal motility, the status of the intestinal mucosa, conditioning regimens including chemotherapy and/or radiotherapy, the hydration status of the patient, and the presence of acute graft-versus-host disease. Therefore, C2 monitoring of oral cyclosporine has not been used in standard hematopoietic stem cell transplant practice except for a small number of studies.[8]

In this study, blood C0 and C2 levels were investigated, and the incidence of adverse effects and biochemical and metabolic effects in relation to drug levels were determined in pediatric hematopoietic stem cell transplant patients in whom cyclosporine was switched to oral microemulsified form after intravenous (IV) administration during the immediate posttransplant period.

## Materials and Methods

Seventy-two patients underwent hematopoietic stem cell transplants at Hacettepe University Faculty of Medicine, Pediatric Bone Marrow Transplantation Unit between 2004 and 2007; C0 and C2 levels were recorded in 28 patients during the period of oral cyclosporine intake. Cyclosporine trough level monitoring is the standard method for monitoring cyclosporine levels at our unit. Considering the effective use of C2 monitoring in organ transplant patients, we started to follow C2 levels for our bone marrow transplant patients as well. Because the literature was based on oral cyclosporine intake, C2 monitoring was done in patients after switching to oral form. Retrospective analysis of C0, C2 levels, and C2/C0 ratio were performed, and all patients who had C0 and C2 level monitoring during oral drug intake were included in this study. Cyclosporine levels during the second hour were not available in outpatients with infrequent clinical visits and in those with difficult intravenous access to draw blood. Therefore, C2 level monitoring was not done on a routine basis.

Prior to the study, the protocol was approved by our local institutional ethics committee and conforms to the ethical guidelines of the 1975 Helsinki Declaration. Written, informed consent was obtained from all of the subjects.

### Patients and Donors

Patient and donor characteristics are shown in Table 1.

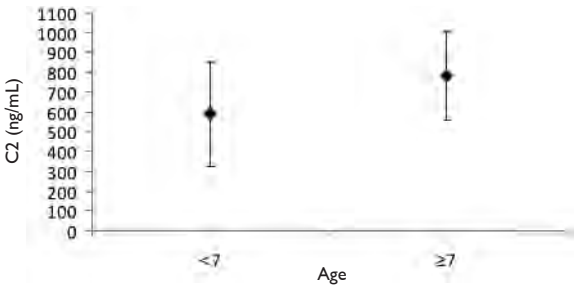


**Figure 1.** Shows the relation between age of the patients (< 7 years of age versus ≥ 7 years of age) and C2 level of cyclosporine ($P < .05$).

Biochemical parameters (creatinine, urea, uric acid, alanine aminotransferase, aspartate aminotransferase, total and direct bilirubin, cholesterol, low-density lipoprotein, triglyceride, sodium, and potassium) were measured before initiation of the conditioning regimen and afterwards at frequent time points. Blood for C0 and C2 levels was obtained in ethylenediaminetetraacetic-acid–containing tubes, C2/C0 ratio was calculated, and

**Table 1.** Patients and donors characteristics.

| | n | % |
|---|---|---|
| Sex | | |
| Male | 20 | 71.5 |
| Female | 8 | 28.5 |
| Age | | |
| ≥ 7 years | 12 | 43.0 |
| < 7 years | 16 | 57.0 |
| Diagnosis | | |
| Malignant diseases | 8 | 28.5 |
| Acute myeloblastic leukemia | 4 | |
| Acute lymphoblastic leukemia | 2 | |
| Chronic myeloblastic leukemia | 1 | |
| Juvenile myelomonocytic leukemia | 1 | |
| Nonmalignant diseases | 20 | 71.5 |
| Thalassemia major | 5 | |
| Aplastic anemia | 4 | |
| Osteopetrosis | 3 | |
| Leukodystrophy | 3 | |
| Fanconi aplastic anemia | 1 | |
| Hemophagocytic syndrome | 1 | |
| Hurler syndrome | 1 | |
| CD3 receptor deficiency | 1 | |
| Congenital dyserythropoietic anemia | 1 | |
| Donor HLA compatibility | | |
| 6/6 | 24 | 85.7 |
| 5/6 | 4 | 14.3 |
| Stem cell source | | |
| Bone marrow | 22 | 78.6 |
| Peripheral blood | 5 | 17.8 |
| Cord blood | 1 | 3.6 |
| Conditioning regimen | | |
| Myeloablative | 21 | 75.0 |
| Nonmyeloablative | 7 | 25.0 |
| Nucleated marrow cell dose | | |
| $\leq 3 \times 10^8$/kg | 2 | 7.2 |
| $> 3 \times 10^8$/kg | 26 | 92.8 |

*Abbreviations:* HLA, human leukocyte antigen

cyclosporine dosages were recorded. In addition to the laboratory values, data related to the disease, transplant procedure, complications (including veno-occlusive disease, acute and chronic graft-versus-host disease, and mucositis, and adverse effects such as hypertrichosis, gynecomastia, and gingival overgrowth) also were recorded.

**Conditioning regimen**

Twenty-one patients received a classic myeloablative regimen, and 7 received a reduced-intensity regimen. As a myeloablative regimen, busulfan (busulfex IV dose was 12.8-16 mg/kg, adopted according to the patient's age) + cyclophosphamide (120-200 mg/kg total dosage) ± melphalan ± antithymocyte globulin ± etoposide were administered. Total body irradiation replaced busulfan in 1 patient. Cyclophosphamide ± fludarabine ± antithymocyte globulin ± low-dose busulfan (6 mg/kg, total dosage) combinations were used in patients who received a reduced-intensity regimen.

**Graft-versus-host disease prophylaxis**

The patients were initiated on IV cyclosporine at a daily dosage of 3 mg/kg in 2 divided doses from day -1 before the hematopoietic stem cell transplant. After improvement of the nutritional state and mucositis, patients began receiving the oral microemulsion form at twice the IV dose. All patients received micro-emulsified cyclosporine. Cyclosporine dosage adjustments were based on biweekly standard C0 measurements to achieve C0 of 150 to 250 ng/mL. Tapering of cyclosporine was started 1 to 3 months after hematopoietic stem cell transplant and discontinued at 3 to 6 months or at 9 to 12 months in patients with thalassemia or aplastic anemia in the absence of graft-versus-host disease.

Adjunctive prophylactic therapy against graft-versus-host disease consisted of methotrexate (n=24) at a dosage of 10 mg/m$^2$ on days +1, +3, and +6. Methylprednisolone therapy was given to 1 patient who underwent a cord blood transplant. Methylprednisolone also was administered at a dosage of 2 mg/kg/d IV to patients who developed graft-versus-host disease. Three patients received mycophenolate mofetil for graft-versus-host disease treatment. Oral ciprofloxacin, fluconazole, intravenous immunoglobulin, and acyclovir were administered as supportive therapy. Trimethoprim sulfamethoxazole also was administered after engraftment.

**Cyclosporine concentration measurements**

The C0 and C2 levels were measured in peripheral blood samples before and 2 hours after the oral intake of the morning doses. Cyclosporine concentration was analyzed using the AXY5YM (Diagnostic Division, Abbott Laboratory, Abbott Park, IL, USA) by fluorescence polarization immune assay. Values corresponding to 0 to 300 ng/mL were considered in the reference range.

**Definitions**

Acute graft-versus-host disease was diagnosed from clinical findings, and/or biopsies from skin, or gastrointestinal system, and graded according to the Glucksberg scoring system.[9] Chronic graft-versus-host disease was diagnosed in those patients who had graft-versus-host disease findings 100 days after a hematopoietic stem cell transplant,[10] and was graded as limited or extensive. Veno-occlusive disease or sinusoidal obstruction syndrome was defined according to Seattle criteria.[11] Grading of mucositis was done according to Common Toxicity Criteria (National Cancer Institute, 2002).[12] An increase and darkening in hairiness in areas outside the virilizing hairy regions (beard, moustache, and genital region) was defined as hypertrichosis. Gingival overgrowth was recognized as an abnormal gingival puffiness and protrusion toward the tooth. Gynecomastia was described as an enlargement in the mammary tissue when compared to normal growth.

**Statistical Analyses**

Statistical analyses were performed with SPSS software for Windows (Statistical Product and Service Solutions, version 11.5, SSPS Inc, Chicago, IL, USA). Pearson product moment correlation coefficient was used to study the relation between 2 numeric variables. The Mann-Whitney *U* test was performed to determine a difference in the cyclosporine dose/weight values between the groups. A Kruskal-Wallis test was used to compare more than 2 groups. A $P$ value ≤ .05 was considered statistically significant.

## Results

Both C0 and C2 analyses were performed on 113 samples in 28 patients between days 13 and 64 after a hematopoietic stem cell transplant. The mean oral

dosage of cyclosporine was 5.5 ± 1.7 mg/kg/d (range, 2.1-8.8 mg/kg/d). Median C0 and C2 levels were 153.3 ± 58.1 ng/mL (range, 82.8-294.0 ng/mL) and 672.1 ± 259.8 ng/mL (range, 215.0-1229.0 ng/mL). Mean C2/C0 ratio was 4.8 ± 1.2 (range, 2.3-7.1). A statistically significant correlation was determined between C0 and C2 levels (as expected) with Pearson correlation analyses ($P < .001$, r: .0795). The mean transition day from the cyclosporine IV to oral form was +18.0 ± 3.4 day (between days 10 and 24) after a hematopoietic stem cell transplant. Mean neutrophil engraftment day was 16.0 ± 4.0 (range, 9-26). No statistically significant relation was determined between the transition from IV to the oral form of cyclosporine and the engraftment day ($P > .05$).

**Table 2.** Relation between biochemical parameters and C0, C2 levels, and C2/C0 ratio.

| | C0 (ng/mL) | | C2 (ng/mL) | | C2/C0 | |
|---|---|---|---|---|---|---|
| | *P* | r | *P* | r | *P* | r |
| Na | .096 | .001 | .0285 | .02 | .051 | .037 |
| K | -.026* | -.042 | .000** | -.064 | .072 | -.034 |
| Urea | .067 | .083 | .095 | .01 | .035 | -.018 |
| Creatinine | .038* | .039 | .02* | .043 | .049 | .013 |
| Uric acid | .04 | .016 | .035 | .018 | .096 | .01 |
| Triglyceride | .035 | .018 | .038 | .017 | .069 | .07 |
| Cholesterol | .019 | .025 | .061 | .01 | .055 | -.011 |
| Low-density lipoprotein | .061 | .038 | .048 | .014 | .048 | -.014 |
| Alanine aminotransferase | .082 | -.043 | .061 | .01 | .042 | .015 |
| Aspartate aminotransferase | .072 | -.06 | .08 | .04 | .073 | .06 |
| Total bilirubin | .028 | -.021 | .063 | -.09 | .035 | .018 |
| Direct bilirubin | .059 | -.01 | .089 | .02 | .037 | .017 |

***Abbreviations:*** K, potassium; Na, sodium
*$P \leq .05$ **$P < .001$

A statistically significant positive relation was determined between C0 or C2 levels and serum creatinine values ($P < .05$ for both). A statistically significant negative relation was observed between C0 and C2 levels and serum potassium levels ($P < .05$ and $P < .001$). Further analyses failed to reveal a statistically significant relation between C0, C2 levels, C2/C0 ratio, and other biochemical parameters (Table 2).

When patients were divided into 2 groups according to age, those < 7 years old showed significantly lower C2 levels when compared with those of the older patients ($P < .05$) (Table 2, Figure 1).

No statistically significant relation was noted between sex and C0 and C2 levels, although C0 levels of the girls (170 ng/mL) were higher than those of the boys (146 ng/mL) (Table 3). The analysis of cyclosporine levels of the patients with malignant and nonmalignant diseases did not reveal a statistically significant difference ($P > .05$). Patients with malignant diseases were more prone to have higher C0 levels (168 vs 146 ng/mL) (Table 3). Among 8 patients with acute graft-versus-host disease, mean C0 levels were found to be higher than those of the patients without graft-versus-host disease (195.4 ± 58.3 vs 136.5 ± 5.01 ng/mL), indicating a dosage adjustment based on C0 levels ($P < .05$) (Figure 2). However, a significant relation was not detected between acute graft-versus-host disease and C2 levels and C2/C0 ratio. Additionally, if cyclosporine levels of 5 patients who later developed chronic graft-versus-host disease were compared with those of patients without chronic graft-versus-host disease, no statistically significant relation was found between C0, C2 levels, or C2/C0 ratios (Table 3).

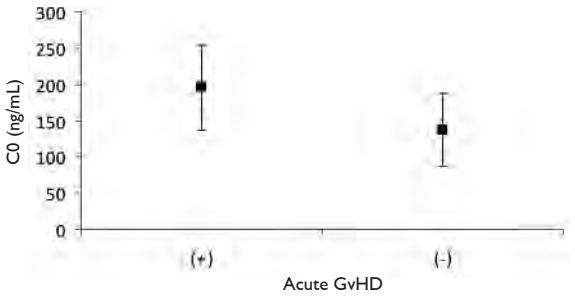


**Figure 1.** Shows the relation between acute graft-versus-host disease and C0 level of cyclosporine ($P < .05$)

Veno-occlusive disease developed in 3 patients (1.07%), and grade 3 to 4 mucositis was observed in 13 patients (46.4%). Mean C0, C2 levels, and C2/C0 values of the 3 patients with veno-occlusive disease were 103, 544, and 5.3 ng/mL, while these values in the 25 patients without veno-occlusive disease were 159, 687, and 4.8 ng/mL (Table 3). The intensity of the conditioning regimen, whether a classic myeloablative regimen (including busulfan) or reduced-intensity regimen demonstrated no statistically significant influence on C0, C2 levels, or C2/C0 ratios, although the C0 and C2 levels of the patients in the reduced-intensity conditioning regimen group tended to be higher than those of the classic regimen group (C0: 174.1 ± 7.08 vs

146.38 ± 53.4 and C2: 746.7 ± 311.1 and 647.3 ± 243.9) ($P > .05$) (Table 3).

**Table 3.** Relation between biochemical parameters and C0, C2 levels, and C2/C0 ratio.

| | | | | |
|---|---|---|---|---|
| Sex | | | | |
| Girl | 8 | 17.02 ± 44.3 | 692.2 ± 239.5 | 4.6 ± 1.2 |
| Boy | 20 | 146.5 ± 62.5 | 664.0 ± 273.0 | 5 ± 1.1 |
| *P* | | > .05 | > .05 | > .05 |
| Age (y) | | | | |
| < 7 | 16 | 137.9 ± 54.5 | 588.8 ± 261.9 | 4.5 ± 1.2 |
| ≥ 7 | 12 | 173.7 ± 58.6 | 783.1 ± 22.04 | 5.2 ± 1.1 |
| *P* | | > .05 | ≤ .05 | > .05 |
| Type of disease | | | | |
| Malignant | 8 | 168.4 ± 63.2 | 702.3 ± 255.5 | 4.5 ± 1.1 |
| Nonmalignant | 20 | 146.1 ± 55.8 | 657.8 ± 267.5 | 5.0 ± 1.2 |
| *P* | | > .05 | > .05 | > .05 |
| Acute graft-versus-host disease | | | | |
| (+) | 8 | 195.3 ± 58.3 | 792.6 ± 23.0 | 4.3 ± .08 |
| (-) | 20 | 136.4 ± 5.01 | 623.9 ± 26.05 | 5.0 ± 1.2 |
| *P* | | ≤ .05 | > .05 | > .05 |
| Chronic graft-versus-host disease | | | | |
| (+) | 5 | 195.5 ± 58.0 | 811.5 ± 263.5 | 42.8 ± .05 |
| (-) | 23 | 144.1 ± 54.9 | 641.8 ± 254.6 | 5.0 ± 1.2 |
| *P* | | > .05 | > .05 | > .05 |
| Veno-occlusive disease | | | | |
| (+) | 3 | 103.4 ± 19.8 | 544.4 ± 161.6 | 5.3 ± .09 |
| (-) | 25 | 159.3 ± 58.4 | 687 ± 267.3 | 4.8 ± 1.2 |
| *P* | | > .05 | > .05 | > .05 |
| Conditioning regimen | | | | |
| Classic | | | | |
| Myeloablative | 21 | 146.38 ± 53.4 | 647.28 ± 243.9 | 4.9 ± 1.3 |
| Reduced | | | | |
| intensity | 7 | 174.1 ± 7.08 | 746.7 ± 311.1 | 4.5 ± .08 |
| *P* | | > .05 | > .05 | > .05 |

Hypertrichosis, gingival overgrowth, and gynecomastia were observed in 20 (71.4%), 11 (39.3%), and 4 patients (14.3%). However, no significant relation was found between those adverse effects and C0, C2 levels, C2/C0 ratio, and dosage (mg/kg) administered. None of the patients developed significant neurotoxicity in this group except for a mild hand tremor.

The mean cyclosporine dosage administered by the oral route was 5.5 ± 1.7 mg/kg/d (range, 2.1-8.8 mg/kg/d). No statistically significant relation was found between the administered dosage and age, sex, acute and chronic graft-versus-host disease, mucositis, development of veno-occlusive disease, the conditioning regimen, and malignant or nonmalignant disease state. An inverse correlation was determined between cyclosporine dosage and C0 levels ($P < .05$), whereas no statistically significant relation was determined between cyclosporine dosage and C2 levels or C2/C0 ratio (Table 4) (Figure 1). Analysis of the correlation between biochemical parameters and orally administered cyclosporine dosage also failed to show a statistically significant relation ($P > .05$) (Table 4).

**Table 4.** Relation between cyclosporine dosage and C0, C2 levels, C2/C0 ratio, age, sex, acute graft-versus-host disease, chronic graft-versus-host disease, mucositis, and veno-occlusive disease.

| | Oral cyclosporine dosage (mg/kg) *P* |
|---|---|
| C0 | -.03* |
| C2 | .036 |
| C2/C0 | .028 |
| Age | .071 |
| Sex | .033 |
| Acute graft-versus-host disease | .095 |
| Chronic graft-versus-host disease | .069 |
| Mucositis | .036 |
| Veno-occlusive disease | .048 |

*$P < .05$

## Discussion

Despite the advantages of cyclosporine in hematopoietic stem cell transplants and solid organ transplants, the drug may have toxic effects on several organs. Nephrotoxicity is the most-frequent toxic effect of the drug. A proportional increase in serum creatinine, urea, and uric acid levels has been reported with increasing serum cyclosporine levels. These levels can normalize after necessary adjustments are made to the cyclosporine dosage.[13] Although creatinine clearance has been accepted as a reliable criterion for renal function, blood urea and creatinine levels are widely used in practice because frequent determination of creatinine clearance is not practical.[14] In the present study, a significant positive relation was determined between C0-C2 levels and serum creatinine levels, and the correlation was particularly important for C2 levels. Because C2 levels represent the highest levels of the drug achieved with sudden absorption after oral intake, it can be suggested that C2 level monitoring may be useful for preventing nephrotoxicity in pediatric hematopoietic stem cell transplant patients.

Another well-known effect of cyclosporine is hyperpotassemia and hyponatremia attributed to hypoaldosteronism, which has an influence on Na-K-ATPase pumping.[15] However, other studies have shown normal aldosterone levels associated with hyperpotassemia in patients who underwent a hematopoietic stem cell transplant.[16]

In the present study, a negative relation between C0-C2 levels and serum potassium levels was detected, and a significant correlation was

determined between C2 levels and hypopotassemia. Hypopotassemia owing to cyclosporine administration is rare and was reported in patients who underwent a renal transplant process and received cyclosporine.[17] Nevertheless, a significant relation between cyclosporine and sodium levels was not detected in the present study. Our findings (excluding inhibition of Na-K-ATPase pumping mechanism owing to cyclosporine administration) suggest a different mechanism of renal toxicity and/or the presence of multiple drug interactions that might have played a role in developing hypokalemia.

It has been reported that hepatotoxicity usually develops in patients with long-term cyclosporine administration.[18] In the present study, no statistically significant relation was determined between mean alanine aminotransferase, aspartate aminotransferase, total/direct bilirubin values and C0, C2 levels, and C2/C0 ratio. An increase in cholesterol, triglyceride, and low-density lipoprotein levels was present in our patients; however, no significant relation with cyclosporine levels was determined.

Age plays an important role for excretion of cyclosporine from the blood. Studies have shown that cyclosporine clearance reaches a peak level at 10 years of age, and then gradually decreases as the patient reaches adolescence.[19] In our study, cyclosporine levels in patients < 7 years of age were lower when compared with patients who were ≥ 7 years of age, and this difference was found to be statistically significant for C2 levels. The disparity arises from differences in cyclosporine metabolism changing with age. However, we did not find any difference in respect to the clinical outcome including engraftment days, veno-occlusive disease, acute and chronic graft-versus-host disease, mucositis, and adverse effects such as hypertrichosis, gynecomastia, and gingival overgrowth between the patients < 7 years of age and those ≥ 7 years of age.

The importance of the cyclosporine plasma level remains controversial. It has been shown that when the C2 peak level is 800 to 2285 ng/dL 2 hours after administration of the drug, it inhibits calcineurin at 70% to 96% and suppressed IL-2 release from T cells.[19] Information related with C0 and C2 values of patients who underwent a solid organ transplant is controversial.[20] There are a limited number of studies related with C2 monitoring in patients with a hematopoietic stem cell transplant. Hendriks and associates[21] have shown that a C2 level of > 800 ng/dL is sufficient for calcineurin inhibition. In another study by Schmidt and associates,[22] graft-versus-host disease risk decreased in patients with cyclosporine serum level over 250 ng/dL, and in another study by Martin and associates,[23] increased graft-versus-host disease risk was observed in children with a cyclosporine level below 85 ng/dL but not in those with a level of 110 ng/dL during the first 2 to 3 weeks after transplant. Cyclosporine levels were found to be considerably low in children when compared with adults. Cyclosporine levels are closely related to the oral intake of patients and presence and degree of mucositis; therefore, the IV form of cyclosporine is used until regression of mucositis and improvement in oral intake. Graft-versus-host disease-associated gastrointestinal inflammation, increased capillary permeability, and reduced multiple-drug resistance in the intestinal vein epithelium may interfere with cyclosporine excretion, thus increasing blood cyclosporine levels.[24] In a study carried out by Barkholt and associates,[8] no relation was detected between acute graft-versus-host disease and C2 levels.

It is well known that the metabolism and clearance of cyclosporine can be affected by several drugs.[3] In the present study, C0 and C2 levels were found to be considerably lower in patients who received a classic busulfan-containing conditioning regimen when compared with those who received a reduced-intensity conditioning regimen. Because cyclosporine levels of patients were studied at least 2 weeks after the end of the conditioning regimen, it is unlikely that busulfan had a direct effect on the levels; however, this finding was attributed to the level of tissue injury, mucositis, and inflammatory cytokine levels. In the present study, cyclosporine dosage was not affected by C2 level or C2/C0 ratio but showed a negative relation with C0 level. This finding is derived from the standard cyclosporine dosage adjustment made according to C0 levels in our patients. Dosage adjustment based on C2 levels was not practical owing to lack of reference values for hematopoietic stem cell transplant patients as opposed to solid organ transplants.

In summary, C2 levels were measured during oral cyclosporine intake in pediatric hematopoietic stem cell transplant patients, and the relations of C0, C2 levels, C2/C0 ratio, and cyclosporine dosage with

cyclosporine-related effects/events were evaluated in this study. Cyclosporine levels during the second hour were found significantly lower in children younger than 7 years old, confirming increased clearance in younger ages. Cyclosporine levels during the second hour were significantly correlated with blood creatinine values, suggesting C2 level monitoring may be a useful parameter for preventing renal toxicity. However, C0 levels also showed a positive correlation with blood creatinine values and a significant positive relation was determined between C0 and C2 levels. Furthermore, there are a few studies about C2 level monitoring suggesting optimal C2 levels in children who underwent a hematopoietic stem cell transplant. Therefore, routine use of C2 level monitoring was not really better than C0 level monitoring in children during a hematopoietic stem cell transplant in this study. However, C2 level monitoring still could be useful in selected scenarios including patients with increased risk of renal toxicity or in states where a better estimation of gastrointestinal absorption is needed.

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