Drug Utilization Evaluation of Cyclosporine in Allogeneic Hematopoietic Stem Cell Transplantation

Mahshid Mehdizadeh,1 Abbas Hajifathali,1 Ali Tafazoli2

Abstract

Objectives: The use of cyclosporine for graft-versus-host disease prophylaxis is a major factor in successful allogeneic hematopoietic stem cell transplantation. However, despite the drug being in clinical practice for more than 3 decades, there is no current global and consistent protocol for its optimal method of administration. In this study, we recorded situations related to cyclosporine administration and associated adverse reactions to aid in the development of more precise future guidelines.

Materials and Methods: We monitored 22 candidates for allogeneic stem cell transplant during their hospitalization for a 1-year period, acquiring data recorded from predefined questionnaires prepared according to accredited literature, which included daily clinical and laboratory examinations.

Results: Despite active attempts toward adherence to a standard protocol for cyclosporine administration, we found numerous occasions of deviations or mistakes, which may have led to adverse reactions.

Conclusions: Our study, as one of the first published "drug utilization evaluations" for cyclosporine in stem cell transplant setting, proposes that educating involved clinical staff regarding a standard method of cyclosporine administration and providing efficient facilities would be highly valuable to implementation of a better practice.

Key words: Cyclosporine, Drug utilization review, Hematopoietic stem cell transplantation

Introduction

Graft-versus-host disease (GVHD) is the most frequent complication after allogeneic hematopoietic stem cell transplant (HSCT), which is triggered by immunocompetent donor cells with high rates of morbidity and mortality.1,2 Immunosuppressive therapy based on cyclosporine (CsA) is a common regimen after this kind of transplant. Cyclosporine has a narrow therapeutic index,3 and it is common for patients to require multiple dose alterations during the early posttransplant period. Elevated CsA concentrations are associated with significant toxicity and often result in the temporary cessation or discontinuation of the drug. Low blood concentrations also result in significant immunologic risks, primarily GVHD and loss of stem cell graft. The pharmacokinetics of CsA is also highly complex, and maintaining therapeutic and safe concentrations is a very challenging issue.4 Failure or delay in achieving the blood concentration targets can result in renal dysfunction, hypertension, hyperglycemia, and central nervous system or infectious toxicities, as well as serious immunologic complications such as GVHD or poor engraftment. Therefore, it is important to observe and control all aspects of CsA administration.

Because of the high frequency of nephrotoxicity and other adverse reactions with CsA administration, we conducted a drug utilization evaluation (DUE) study to evaluate the appropriateness of CsA administration for GVHD prophylaxis in HSCT patients in accordance with available literature. To our knowledge, a similar study has so far not been conducted; therefore, a drug use evaluation of CsA could provide value in this setting.

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Materials and Methods

We prospectively observed all candidates for allogeneic bone marrow transplant in Taleghani Hospital of Shahid Beheshti Medical University (Tehran, Iran) between 2013 and 2014. Patients from 18 to 65 years old were included in our study. However, patients with baseline sepsis and uncontrolled infection and liver and kidney dysfunction (serum creatinine and total bilirubin more than 1.5 times the normal upper limit) were excluded.

We based the standard protocol for GVHD prophylaxis on the European Group for Blood and Marrow Transplantation-European Leukemia Networking Group recommendations and on the US Food and Drug Administration instructions for CsA administration, with adverse reactions graded in accordance with National Cancer Institute tables.5

All data were recorded with the use of predefined questionnaires, which included patient demographic characteristics, drug history, medical background, and laboratory tests before and after hospital admission. Kidney and liver function tests, blood lipid and glucose levels, and clinical observation of neurotoxicity and hypertension were the focus of our analysis. Clinical outcomes of patients for occurrence of GVHD or veno-occlusive disease were also assessed daily. Data related to drug administration were recorded separately and included duration of infusion, infusion type, carrier solutions, and acute infusion reactions.

This study was approved by the Ethical Review Committee of our university hospital. All of the protocols conformed to the ethical guidelines of the 1975 Helsinki Declaration. Written informed consent was obtained from all patients.

To reach our goal to produce a pilot DUE, data projection analyses were performed with SPSS software (SPSS: An IBM Company, version 17.0, IBM Corporation, Armonk, NY, USA). The “analyze” tab in the software was used to obtain basic descriptive statistics of our data. For “scale” data, such as age, height, weight, dosing and administration parameters, and laboratory measurements, we used the “descriptive” command, implemented for achieving mean, median, and standard deviation values. For “categorical” data, including rate of occurrence of adverse effects, we used the “frequencies” command. Results are shown as mean ± SD.

Results

We analyzed the data of 22 patients for this study, which included 12 men (50%) and 12 women (50%) with mean age of 30.23 ± 7.746 years (range, 21-50 y) and mean height of 1.66 ± 0.10 m. There were only 2 non-Iranian patients. Underlying diseases included acute myeloid leukemia, acute lymphoblastic leukemia, non-Hodgkin lymphoma, and aplastic anemia (Table 1).

| Table 1. Frequency of Underlying Disease in Study Candidates for Allogeneic Transplant |
|-----------------------------------------------|---------------------|----------------------|
| Diagnosis          | Number of Patients | Percentage |
| AML               | 12                  | 54.5%     |
| ALL               | 8                   | 36.4%     |
| NHL               | 1                   | 4.5%      |
| AA                | 1                   | 4.5%      |
| Total             | 22                  | 100%      |

Abbreviations: AA, aplastic anemia; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; NHL, non-Hodgkin lymphoma

In our analysis of drug administration status, we found that loading dose was not administered for any patient. In addition, infusion pump was only used in 8 of the transplant patients. Mean duration of infusion was 1.72 ± 0.55 hours (range, 0.8-3 h). All patients received CsA in normal saline solution through hospital-grade plastic tubing. Approximately 86% of the patients received their doses exactly 12 hours after the previous dose with the use of spot monitoring.

Cyclosporine was administered at intravenous doses ranging from 120 mg/day to 250 mg/day (mean, 99.6 ± 19.7 mg/dose). A transition from intravenous infusion to oral intake occurred after patient stabilization and oral tolerability with a mean of 13.8 days after transplant (range, 10-25 d). An overdose error (more than twice the ordered dose) in a single administration occurred for 1 patient. Data regarding drug administration are shown in Table 2.

| Table 2. Cyclosporine Administration Information of Study Candidates for Hematopoietic Stem Cell Transplant |
|-----------------------------------------------|---------------------|----------------------|
| Diagnosis          | Number of Patients | Percentage |
| Infusion type       |                      |          |
| Pump               | 8                    | 36.4%     |
| Hanging IVIB       | 14                   | 63.6%     |
| Duration of infusion |                      |          |
| Less than 2 h      | 10                   | 45.5%     |
| More than 2 h      | 2                    | 9%        |
| Exactly 2 h        | 10                   | 45.5%     |
| Dose               |                      |          |
| Correct dose       | 21                   | 95.5%     |
| Overdose           | 1                    | 4.5%      |

Abbreviations: IVIB, intravenous infusion bag
Laboratory observations showed that CsA achieved a mean trough level of 225.2 ± 69.9 ng/mL about 12 hours after a specified dose. A single occasion of subtherapeutic level was shown in 3 patients (13.6%) and double occasions in 1 patient (4.5%), whereas supratherapeutic levels occurred in 7 patients (31.8%) on a single occasion, 2 patients (9.1%) on a double occasion, and 1 patient (4.5%) on a triple occasion. Only 10 patients (about 45%) had levels that were constantly within the therapeutic range during their admission period. Modifications for dosing based on drug levels and other laboratory findings occurred for 8 patients (36.4%).

Regarding the occurrence of adverse reactions, a temporary hold of CsA was ordered for 1 patient as a result of nephrotoxicity. Infusion reactions included hot flashes (3 patients), rigor (1 patient), nausea (8 patients), paresthesia (3 patients), and headache (2 patients).

Kidney-related observations revealed a mean baseline serum creatinine level of 0.81 ± 0.06 mg/dL (range, 0.7-0.9 mg/dL). Acute kidney toxicity occurred in 4 patients (1 each at grades 1 and 3 and 2 at grade 2). No permanent injury due to CsA therapy was recorded. Coadministration of nephrotoxic drugs, specifically amphotericin (13 patients) and amino-glycosides (12 patients), also was recorded.

Neurotoxicity classification of patients by National Cancer Institute toxicity criteria showed 18.2% with grade 1 reactions, 9.1% with grade 2 reactions, 9.1% with grade 3 reactions, and 13.6% with grade 4 reactions. Four patients had at least 1 occasion of posttherapy hypertension (all National Cancer Institute grade 1). No patient required pharmacologic measures after neurotoxicity.

Regarding metabolic alterations, dyslipidemia was found in about 95% of patients, consisting of 18 patients with hypertriglyceridemia (triglyceride level > 150 mg/dL) and 15 patients with hypercholesterolemia (low-density lipoprotein cholesterol level > 100 mg/dL). Therapy for correction was considered for 1 patient. All patients showed hyperglycemia at least in 1 occasion during admission, but only 7 patients (31.8%) received therapy. Metformin use was recorded for 1 patient, and all others received insulin. With the use of National Cancer Institute grading, 3 patients had grade 1, 8 patients had grade 2, 9 patients had grade 3, and 1 patients had grade 4 reactions. Table 3 shows the frequency of adverse reaction occurrence.

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Number of Patients (%)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusion reaction</td>
<td>8 (36.4%) 2 (9.1%) 1 (4.5%) 0 11</td>
<td></td>
</tr>
<tr>
<td>Nephrotoxicity</td>
<td>1 (4.5%) 2 (9.1%) 1 (4.5%) 0 4</td>
<td></td>
</tr>
<tr>
<td>Neurotoxicity</td>
<td>4 (18.2%) 2 (9.1%) 2 (9.1%) 3 (13.6%) 11</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>4 (18.2%) 0 0 0 4</td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>3 (13.6%) 8 (36.4%) 9 (40.9%) 1 (4.5%) 21</td>
<td></td>
</tr>
</tbody>
</table>

Observations for clinical outcomes showed 7 patients with acute GVHD (1 patient with grade 1 and 1 with grade 2, 3 patients with grade 3, and 2 patients with grade 4), with only 1 occurrence of veno-occlusive disease during admission. All occurrences of GVHD were controlled with therapeutic measures; however, the patient with veno-occlusive disease died after a second admission.

Work-up for mucositis showed 8 patients with mild, 10 patients with moderate, and 2 patients with severe mucositis, according to the Common Terminology Criteria for Adverse Events grading.

Regarding outcomes, 2 patients died, which were caused by relapse of underlying disease and veno-occlusive disease.

Discussion

Cyclosporine administration is the standard regimen for GVHD prophylaxis in HSCT recipients. Cyclosporine therapy has resulted in a significant decrease in GVHD occurrences with better clinical outcomes. The European Group for Blood and Marrow Transplantation is a major foundation that publishes guidelines for HSCT and specifically GVHD management, and their recommendations have been used in our center during the study. In addition, we applied US Food and Drug Administration prescribing information for CsA drug administration.

Results showed that, despite attempts to treat in accordance with guidelines, deviations in drug administration management were notable. According to the guidelines, CsA levels should be between 100 ng/mL and 300 ng/mL, especially during the initial posttransplant period. However, during our study, we found several occasions of drug level values out of this range without any dose modification. Probable causes could be as a result of clinical staff being unaware of drug administration protocols, lack of adequate and meticulous monitoring routines, and unreliability of laboratory test results.
A major pitfall observed for intravenous CsA administration was frequent occasions of shorter infusion times than the minimum 2-hour recommendation endorsed by prescribing instructions. Again, this could be due to nursing staff being unaware of instructions, limited number of supervisory personnel, insufficient number of infusion pumps, malfunction of these devices, and easy manipulability of gravity fill infusion sets by unobserved curious patients. Further variability in administration orders also could be the result of variations in protocols for different centers and studies.

A probable explanation for the high number of infusion reactions is the faster than standard infusion rate. As stated by Gupta and associates, rate of infusion can influence pharmacokinetics of CsA and consequently be associated with (peak) concentration-dependent adverse effects.7 This fact has also been confirmed in animal studies.8

Some studies have shown that nephrotoxicity, neurotoxicity, hypertension, and metabolic abnormalities from CsA could be dose or concentration dependent.9-11 Interestingly, these adverse reactions were not more frequent in patients with higher mean blood concentrations, although the limited number of patients and the low predictive value of CsA trough concentrations used in our study should be taken into consideration.12-14

A close observation of all vital signs and clinical symptoms of patients, which is recommended by label instructions during infusion (specifically during the first 30 min) did not occur for many of our patients because of the limited number of clinical staff. This fact could have affected the number patients who had these reactions.

Liver function test results were not analyzed because of the presence of major intrusive factors other than those from CsA administration, such as veno-occlusive disease or GVHD and therapy with conditioning chemotherapy regimens and other hepatotoxic agents like azole antifungal agents. In addition, hyperuricemia, which is a well-known complication of CsA, was not of our concern because of stronger causes for it in our population such as frequent hemolysis episodes during chemotherapy and transfusions.

Hypertension frequently occurs among patients who have received allogeneic HSCT.15 Blood pressure could be increased soon after administration of CsA. Specific vascular changes lead to systemic and renal vasoconstriction and consequently hypertension.16 In our study, hypertension was observed in almost all of the patients; however, because of transient alterations, no therapy was implemented and this was not detectable without our twice daily measurements policy.

Neurotoxicity is an adverse reaction shown in the posttransplant setting, with 50% of our patients having mild to severe symptoms of neurotoxicity. Severe neurotoxicity includes symptoms of confusion, disorientation, decreased responsiveness, visual hallucinations, delusions, seizures, pyramidal motor weakness, cortical blindness, aphasia, and ataxia. Severe neurotoxicity has been reported in 4% to 11% of HSCT patients17,18 and at both therapeutic and high CsA levels.17,19,20 Therefore, routine clinical examination or even interviewing patients would be highly valuable in detecting such effects.

Dyslipidemia is another serious complication that can influence the long-term survival of transplant patients. Dyslipidemia and other cardiovascular risk factors are increased in allogeneic HSCT patients. The risk for allogeneic transplant exceeds that for autologous transplant, perhaps because of differences in immunosuppressive regimens. Low-density lipoprotein cholesterol is a major factor for cardiovascular risk modification, although treatment for severe hypertriglyceridemia is highly recommended. Low-density lipoprotein cholesterol goals were stratified in our study by the National Cholesterol Education Program ATP-III guideline. Statin therapy, recommended as the first-line treatment for high low-density lipoprotein cholesterol dyslipidemia, is also recommended for HSCT patients.21 In our study, 95% of patients showed dyslipidemia but only 1 patient received relevant therapy. One reason was reluctance of clinicians to further complicate the polypharmacy of patients and pending alterations in laboratory results. Reminding patients of postdischarge lipid profile follow-up and implementation of evidence-based therapies could significantly affect the long-term outcomes of patients.

Similar to that shown in our study population, HSCT recipients frequently require parenteral nutrition and immunosuppressive drugs that impose the risk of hyperglycemia.22 Cyclosporine may have deleterious effects on glucose metabolism. Studies have shown that CsA treatment could cause impairment of both synthesis and secretion of insulin,
increased insulin clearance, and alterations in insulin sensitivity.\textsuperscript{23} Strict glucose control has resulted in improved patient outcome.\textsuperscript{24} Although all of our patients had at least 1 episode of hyperglycemia, only 7 of 22 took insulin or metformin for treatment, which was totally effective.

Renal insufficiency is a common complication and a major concern early after HSCT.\textsuperscript{25} The available evidence indicates that CsA represents a risk factor for the occurrence of nephrotoxicity, particularly when combined with amphotericin B or aminoglycosides, agents commonly used in this population.\textsuperscript{26} In our study, CsA was administered simultaneously with amphotericin and aminoglycosides (gentamicin or amikacin) in about 59\% and 54\% of patients, with 4 patients on these combinations developing renal dysfunction. Reasonably, 3 patients with a triple combination involved grade 2 and grade 3 kidney toxicities, 1 patient who was receiving only aminoglycoside had grade 1 reaction, but no one with only CsA therapy experienced acute injury. Therefore, close monitoring of renal function in HSCT patients is a rational endeavor because of the high risk of occurrence in such patients with multiple risk factors.

According to these findings, early discovery of adverse reactions or even making predictions using previous controlled experiments will positively affect the timely decision to implement supportive or therapeutic measures.

For clinical evaluations, it could be stated that, although GVHD occurred in high numbers in our patients, CsA is still the first choice for GVHD prophylaxis because of long-term experience, evidence-based support, and financial concerns.\textsuperscript{27,28}

In conclusion, we note that, because of the importance of GVHD management in HSCT patients, the involved clinical professionals should be familiar with the appropriate dose and standard administration approaches. The value of education for the clinical team and even for the patient about disciplines of drug therapy with this vital agent could not be overemphasized. In addition, preparation of adequate and high-quality administration devices would be highly useful in achieving the most optimal and accessible outcome. These results revealed that the hospital staff did not totally comply with predefined protocols of CsA administration; therefore, the presence of a specialized clinical pharmacist would be valuable in this setting for double checks, notifications, and treatment modifications. In parallel, developing modified and updated guidelines with higher applicability and rememberability would be beneficial for patient outcomes. The close observation of CsA clinical behavior and patient response via different types of studies would provide great value in guiding the treatment approach of HSCT patients.

References


