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Brief Articles

Risk Factors for Subtherapeutic Tacrolimus Levels after Conversion from Continuous Intravenous Infusion to Oral in Children after Allogeneic Hematopoietic Cell Transplantation

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A B S T R A C T

Tacrolimus (FK506) is a calcineurin inhibitor and is an essential component of many immunosuppressive regimens. The oral bioavailability of tacrolimus may be affected by many factors, including patient age and gender, as well as by drug-drug interactions or genetic polymorphisms in drug metabolism. The dosing recommendations for pediatric allogeneic hematopoietic cell transplantation (alloHCT) recipients have been derived from tacrolimus use in adult solid-organ transplantation patients. Data describing the impact of conversion of i.v. tacrolimus to oral on the incidence of acute graft-versus-host disease (aGVHD) are limited in children after alloHCT. In this study, we describe the incidence of grades II to IV aGVHD after conversion from i.v. tacrolimus to oral tacrolimus and study the clinical factors associated with delayed achievement of therapeutic blood levels. In this retrospective analysis, 68 pediatric patients (median age, 6.7 years; range, .25 to 22 years), underwent alloHCT for malignant and nonmalignant diseases and received tacrolimus and mycophenolate mofetil for aGVHD prophylaxis. Among all patients, the median number of days to achieve therapeutic tacrolimus trough concentration (10 ng/mL to 20 ng/mL) was 7 days (range, 0 to 37 days). Twenty-two patients developed grades II to IV aGVHD and the cumulative incidence of grades II to IV aGVHD in all patients was 32.4% (standard error, .06). On multivariate analysis ethnicity (white versus others: odds ratio [OR], −4.5; 95% confidence interval [95% CI], 1.091 to 18.91; $P = .038$) and ≥ 10 days of subtherapeutic tacrolimus levels in first 30 days on i.v. (OR, −3.8; 95% CI, 1.276 to 11.43; $P = .017$) were significantly associated with delay in achieving therapeutic tacrolimus trough concentration. The impact of race/ethnicity on therapeutic tacrolimus trough concentration in pediatric alloHCT recipients should be further studied prospectively so that individualized dosing plans can be developed.

INTRODUCTION

The success of allogeneic hematopoietic cell transplantation (alloHCT) is limited by the occurrence of acute graft-versus-host disease (aGVHD), a serious and sometimes fatal complication of the treatment process. Despite significant advances in the field of alloHCT, the incidence of aGVHD remains unacceptably high [1]. One of the key challenges faced in the field of pediatric alloHCT today is related to identifying optimal aGVHD prophylaxis. The majority of aGVHD prevention studies have been conducted in adult patients and guidelines for children have been developed by extrapolating results from these adult-based investigations.

Tacrolimus (FK506) is a calcineurin inhibitor and is an essential component of many immunosuppressive regimens [1]. The oral bioavailability of tacrolimus may be affected by many factors, including patient age and gender, as well as by drug-drug interactions or genetic polymorphisms in drug metabolism [2-4]. Because of these and other factors, tacrolimus requires close monitoring to maintain target blood concentrations. The majority of dosing recommendations for pediatric patients have been derived from tacrolimus use in

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adult and pediatric solid-organ transplantation patients. Very few studies have sought to identify the optimal use of tacrolimus in pediatric patients [5-7].

Key differences between adults and children should be considered when developing prophylactic treatment protocols with tacrolimus for aGVHD. One of the most important of these is differences in drug metabolism. It is well documented that, in many cases, pediatric patients require higher doses of medicines than adult patients because of faster drug metabolism. In 2009, Wallin et al. described the pharmacokinetics of tacrolimus in a small group of children (ages .5 to 18 years). Investigators concluded that for pediatric patients, prophylactic treatment with tacrolimus should be initiated with a loading dose and higher baseline starting doses than those used in adult patients [8]. Prezpiorka et al. also demonstrated that tacrolimus pharmacokinetics were age dependent [5]. However, data describing the impact of conversion from i.v. tacrolimus to per oral (PO) on the incidence of aGVHD is even more limited in children after alloHCT. Younger children, especially younger than 6 years old, may have difficulty in taking oral tacrolimus and/or potentially may also have poor absorption or faster metabolism than older children. We hypothesized that younger patients would take a longer time to achieve therapeutic tacrolimus levels after conversion from i.v. to oral.

In an effort to investigate and optimize our approach to aGVHD prophylaxis with tacrolimus, and in the setting of variable dosing guidelines for pediatric patients, we aimed to describe the incidence of aGVHD after conversion from i.v. tacrolimus to oral tacrolimus and to study the clinical factors associated with delayed achievement of therapeutic blood levels.

METHODS

In this retrospective study, the population comprised pediatric patients who underwent alloHCT and received tacrolimus and mycophenolate mofetil (MMF) for aGVHD prophylaxis at the New York-Presbyterian Morgan Stanley Children's Hospital between March 2003 and October 2012. Patients were excluded if they were initially started on oral tacrolimus, had a diagnosis of primary graft failure, developed aGVHD while on i.v. tacrolimus, or if they took longer than 60 days to achieve therapeutic levels while on oral dosing (n = 1). The most common site of aGVHD at our institution is gastrointestinal GVHD; therefore, to avoid the potential confounding impact of impaired gastrointestinal absorption as well as the possible impact of steroids on tacrolimus metabolism [9], we excluded patients who were treated with systemic steroids for grades II to IV aGVHD of any site while on i.v. tacrolimus.

The taper plan for tacrolimus was diagnosis dependent: patients with nonmalignant diseases started tacrolimus taper at day +180, patients with malignant diseases and matched sibling donors started taper on day +100, and patients with malignant diseases and matched unrelated donors or umbilical cord donors, taper was initiated on day +180. Tacrolimus was tapered over a 6- to 8-week period.

Data Collection and Definitions

Data were collected from the electronic medical record by chart review, which was approved by the institutional review board. All tacrolimus levels through day +100 were collected, as were levels of creatinine and total bilirubin at the time of conversion to oral tacrolimus. Per institutional protocol, tacrolimus doses were adjusted to maintain trough levels between 10 ng/mL and 20 ng/mL. *Therapeutic tacrolimus trough concentration* was defined as obtaining tacrolimus levels between 10 ng/mL and 20 ng/mL for 2 consecutive days [10]. *Renal injury* was defined as having a serum creatinine that was twice the baseline level, measured at day 0 at the time of conversion to oral [10,11]. *Liver toxicity* was defined as any total bilirubin level at the time of oral conversion that was greater than 1.5 times the upper limit of normal (>1.95 mg/dL) [10,12]. Concomitant use of azoles was not part of the analysis in this study, as our patients did not receive azoles as part of their supportive care regimens until after day 100 after transplantation. One patient in this study received voriconazole for the treatment of fungal infection. The majority of patients remained hospitalized until therapeutic tacrolimus trough concentration was achieved on oral regimens.

Conditioning Regimens

Preparative regimens included myeloablative conditioning (n = 31, 45.6%), reduced-intensity conditioning (n = 31, 45.6%), and reduced-toxicity conditioning regimens toxicity (n = 23, 33.8%) [10].

The myeloablative conditioning regimens included total body irradiation + cyclophosphamide (120 mg/kg) ± thiotepa (10 mg/kg) or total body irradiation + melphalan (90 mg/m^2 to 135 mg/m^2) and 2 alkylators, i.v. [13] busulfan (12.8 mg/kg to 16 mg/kg) + cyclophosphamide (120 mg/kg to 200 mg/kg) or i.v. busulfan (12.8 mg/kg to 16 mg/kg) + melphalan (135 mg/m^2).

The reduced-toxicity conditioning regimens included fludarabine (150 mg/m^2 to 180 mg/m^2) and i.v. busulfan (12.8 mg/kg to16 mg/kg) ± alemtuzumab (54 mg/m^2) or fludarabine (150 mg/m^2) and cyclophosphamide (200 mg/kg) ± rabbit antithymocyte globulin (r-ATG) [8 mg/kg].

The reduced-intensity conditioning regimens included fludarabine (150 mg/m^2) and i.v. busulfan (6.4 mg/kg to 8 mg/kg) ± r-ATG (8 mg/kg) or fludarabine (150 mg/m^2) and cyclophosphamide (60 mg/kg) ± r-ATG (8 mg/kg).

aGVHD Prophylaxis

All patients received GVHD prophylaxis with MMF and tacrolimus per institutional protocols. MMF was initiated on day +1 after transplantation. Patients were transitioned from i.v. to oral tacrolimus when they met the following standard criteria: having achieved therapeutic levels on i.v. tacrolimus, were tolerating oral intake, and had no signs of acute gut GVHD. We used the currently accepted conversion factor of 4:1 [5]. aGVHD was diagnosed and graded according to the criteria established by Glucksberg et al. [14].

Supportive Care

Patients received standard supportive care measures as we have previously described [10]. Briefly, herpes simplex virus prophylaxis consisted of i.v. acyclovir (250 mg/m^2) every 8 hours from day −5 until engraftment and mucositis of less than or equal to grade II. Initially, fungal infection prophylaxis consisted of i.v. liposomal amphotericin B (3 mg/kg/day) starting on day 0 through days +100, as has been previously described [15]. Since 2007, however, the majority of patients have received i.v. liposomal amphotericin B (1.5 mg/kg) until day 45 and then micafungin (1 mg/kg to 1.5 mg/kg) until day +100 [16]. Cytomegalovirus prophylaxis was administered as we have previously described [17].

Statistical Analysis

Continuous variables were summarized by median and range and their comparison was done by either median scores or Kruskal-Wallis statistic. Categorical variables were summarized by frequency and percentages and their comparison was carried out by either chi-square test or Fisher's exact test. The logistic regression analysis was used to identify risk factors for subtherapeutic levels on conversion to PO and risk factors for aGVHD. A multivariate logistic regression model was built with the factors were significant at .10 level in univariate logistic regression analysis. A P value < .05 was considered significant. The SAS 9.3 software (SAS Institute Inc., Cary, NC) was used for statistical analysis.

RESULTS

The present study is a retrospective analysis of 68 pediatric patients (median age, 6.7 years; range, .25 to 22 years) who underwent alloHCT and received tacrolimus and MMF for aGVHD prophylaxis at the New York-Presbyterian Morgan Stanley Children's Hospital between March 2003 and October 2012. Patients underwent alloHCT for both malignant (n = 31, 45.6%) and nonmalignant (n = 37, 54.4%) diseases. Stem cell sources included 51.5% (n = 35) bone marrow, 38.2% (n = 26) cord blood, and 10.3% (n = 7) peripheral blood stem cells from both related (n = 35, 51.5%) and unrelated (n = 33, 48.5%) donors. The demographic breakdown of the patients was as follows: 23.5% (n = 16) white (non-Hispanics), 38.2% (n = 26) Hispanic, 20.6% (n = 14) black (non-Hispanics), and 17.7% (n = 12) Asian and Arabic. Subject characteristics are listed in Table 1.

The median days after alloHCT for initiating conversion from i.v. tacrolimus to PO was 21 days (range, 2 to 76).The median and average tacrolimus levels on the day of switch from i.v. to PO were 12.5 ng/mL (range, 7.3 ng/mL to 17.5 ng/