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A Time-to-Event Model for Acute Kidney Injury after Reduced-Intensity Conditioning Stem Cell Transplantation Using a Tacrolimus- and Sirolimus-based Graft-versus-Host Disease Prophylaxis

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A B S T R A C T

There is a paucity of data evaluating acute kidney injury (AKI) incidence and its relationship with the tacrolimus–sirolimus (Tac-Sir) concentrations in the setting of reduced-intensity conditioning (RIC) after allogeneic stem cell transplantation (allo-HSCT). This multicenter retrospective study evaluated risk factors of AKI defined by 2 classification systems, Kidney Disease Improving Global Outcome (KDIGO) score and "Grade 0-3 staging," in 186 consecutive RIC allo-HSCT recipients with Tac-Sir as graft-versus-host disease prophylaxis. Conditioning regimens consisted of fludarabine and busulfan (n = 53); melphalan (n = 83); or a combination of thiotepa, fludarabine, and busulfan (n = 50). A parametric model, with detailed Tac-Sir consecutive blood levels, describing time to AKI was developed using the NONMEM software version 7.4. Overall, 81 of 186 (44%) RIC allo-HSCT recipients developed AKI with a cumulative incidence of 42% at a median follow-up of 25 months. Time to AKI was best described using a piecewise function. AKI-predicting factors were melphalan-based conditioning regimen (HR, 1.96; $P < .01$), unrelated donor (HR, 1.79; $P = .04$), and tacrolimus concentration: The risk of AKI increased 2.3% per each 1-ng/mL increase in tacrolimus whole blood concentration ($P < .01$). In multivariate analysis, AKI grades 2 and 3 according to KDIGO staging were independent risk factors for 2-year nonrelapse mortality (HR, 2.8; $P = .05$; and HR, 6.6; $P < .0001$, respectively). According to the KDIGO score, overall survival decreased with the increase in severity of AKI: 78% for patients without AKI versus 68%, 50%, and 30% for grades 1, 2, and 3, respectively ($P < .0001$). In conclusion, AKI is frequent after Tac-Sir–based RIC allo-HSCT and has a negative impact on outcome. This study presents the first predictive model describing time to AKI as a function of tacrolimus drug concentration.

INTRODUCTION

Acute kidney injury (AKI) is a frequent complication after allogeneic stem cell transplantation (allo-HSCT) [1,2], affecting from 10% to 70% of transplant recipients [3-11]. Kidney impairment after allo-HSCT has been shown to negatively influence nonrelapse mortality (NRM) and overall survival (OS) [4,5,7,9,11,12].

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Calcineurin inhibitors (CNI), mainly cyclosporine (CsA) and tacrolimus, used alone or in combination with other immunosuppressive agents are the most common drugs for graft-versus-host disease (GVHD) prophylaxis in allo-HSCT. These drugs have well-known nephrotoxic effects, mostly secondary to their potent vasoconstricting properties and their ability to cause endothelial injury. Both have shown similar incidences of AKI after allo-HSCT [13,14]. A tacrolimus and sirolimus (Tac-Sir) combination has emerged as a promising strategy to prevent GVHD, especially in the reduced-intensity conditioning (RIC) allo-HSCT setting [15]. The Tac-Sir combination has been shown to be more effective and less toxic than sirolimus combined with CsA [16-18]. However, the former may increase the risk of transplant-associated microangiopathy (TAM) and sinusoidal obstruction syndrome of the liver [9,19-21], conditions that are closely linked with the development of AKI.

There is limited information on the association between concentration levels of immunosuppressive agents and the occurrence of renal complications after allo-HSCT. Thus, high levels of sirolimus have been associated with the development of TAM [22], whereas CNIs have direct nephrotoxic effects and can also precipitate or contribute to TAM. To establish the potential role of the concentration-over-time of these agents in causing AKI, an analysis of drug exposure through the measurement of the area under the curve would be required, but its logistical complexity and cost make it unfeasible in "real-life" clinical practice. For these type of analyses, recommendations suggest the application of powerful methods that take into account the dependency and association between longitudinal data (ie, through blood concentrations of tacrolimus and sirolimus) and time-to-event data (ie, AKI) [23]. Fully parametric time-to-event analyses can bring these 2 types of data together into a single model so that the evaluation of the dependence and association between the longitudinal marker and time-to-event permit a better assessment of treatment effect and result in a lower bias and less inefficient estimates compared with the classic Cox model method [23-28].

With this background, we assessed renal function by serum creatinine levels and as estimated glomerular filtration rates (GFRs) calculated by the modification of diet in renal disease equation in a large cohort of patients who underwent RIC allo-HSCT with the Tac-Sir combination as GVHD prophylaxis. We examined the pharmacokinetic–pharmacodynamic relationship between Tac-Sir exposure and the development of AKI through a parametric time-to-event model using longitudinal through blood concentrations of both drugs.

METHODS

A completely detailed methods section is provided in an online supplementary methods section.

Patients

From October 2008 to October 2015, 186 consecutive RIC allo-HSCT recipients in 3 Spanish institutions who received the Tac-Sir combination to prevent GVHD were included in the study. The institutional review boards approved the study, and written informed consent was obtained from all patients according to the Declaration of Helsinki. The study was registered by the Spanish Agency of Medicines and Health Products with the reference code PIN-SIR-2016-01.

Conditioning Regimen and GVHD Prophylaxis

Three RIC regimens were used in this study. Briefly, fludarabine was combined with busulfan for myeloid neoplasm (Flu-Bu, n = 53) or with melphalan for lymphoid neoplasm (Flu-Mel, n = 83) as detailed elsewhere [29]. The third RIC regimen consisted of fludarabine in combination with busulfan and thiotepa (TBF regimen, which was used for both myeloid and lymphoid malignancies, n = 50). The GVHD prophylaxis consisted of Tac-Sir. The planned taper schedule has been described elsewhere [15].

AKI and TAM Definitions

GFR was calculated by the modification of diet in renal disease equation as follows: (GFR [mL/min per 1.73 m^2] = 186 × serum creatinine (mg/L) − 1.154 × age (in years) − .203 (× .742 if female)) [30]. AKI was defined as a decrease of at least 25% of baseline GFR or when creatinine levels rose above the standard values and reached ≥1.5 times the baseline value. AKI was classified on the basis of the new Kidney Disease Improving Global Outcome (KDIGO) classification system proposed in 2012 based on serum creatinine and urine output [31] and also by the "Grade 0-3 staging" definition, based on serum creatinine and estimated GFR, as detailed elsewhere [1] (see Supplementary Figures S1 and S2). TAM was classified as confirmed or probable according to previously defined international criteria [32-34].

Sir-Tac Blood Level Monitoring, Management, and Technical Considerations

Tac-Sir trough blood levels were monitored at least 2 times per week during the first 4 weeks after transplantation or until discharge, weekly until day +100, and thereafter on each outpatient visit. All blood samples were trough concentrations collected before receiving a scheduled dose. Doses were adjusted for target blood levels of 5 to 12 ng/mL for sirolimus and 5 to 10 ng/mL for tacrolimus.

Statistical Data Analysis

The primary objective of the study was the identification of risk factors for the development of AKI. Secondary objectives were the effect of AKI (analyzed as a time-dependent covariate) on OS and NRM according to the 2 classification systems, KDIGO and Grade 0-3 staging.

Nonparametric and Semiparametric Analyses

AKI, NRM, GVHD, TAM, and relapse were estimated by the cumulative incidence method [35,36]. Univariate analyses of the association of clinical risk factors with these transplantation outcomes were calculated using the Gray test. Time-dependent covariates were analyzed by univariate Cox regression models. When any time-dependent covariate was included in the final models, multivariate analyses were performed by Cox proportional hazards regression; otherwise, the Fine and Gray test was used. The probability of OS was estimated from the time of transplantation using Kaplan-Meier curves [37], and univariate comparisons were done with the log-rank test [38,39]. If AKI was found to have an impact on OS in the univariate analysis, a semi-landmark plot was constructed to illustrate visually the effect [40]. Tests of significance were 2-sided, with statistical significance considered as $P \leq .05$. All statistical analyses were performed using SPSS version 20 (SPSS, Chicago, IL) and R version 2.12.2 (The CRAN project: https://www.rstudio.com) with the packages survival v2.36-10, Design 2.3-0, prodlim v1.2.1, and cmprsk v2.2-221.

Parametric Analysis

A parametric survival model describing time to AKI, with emphasis on the potential effect of tacrolimus and sirolimus exposure, after RIC allo-HSCT was developed by means of nonlinear mixed-effects modeling using the NONMEM software version 7.4. The model was developed in 2 steps: (1) a baseline model without any explanatory factors, and (2) thereafter the impact of the study variables was explored and included in the baseline model. To describe the time to AKI, a parametric survival function according to the following equation was used:

$$S(t) = e^{-\int_0^t h(t)dt}$$

The final model was then used to simulate new treatment schedules to explore treatment outcomes with different drug exposure levels in terms of time until AKI.

RESULTS

Patient Characteristics

Patient and transplant characteristics and outcomes are summarized in Table 1. Overall, 186 RIC allo-HSCT recipients with a median age of 58 years (range, 23 to 72) and with hematologic malignancies, mostly with acute leukemia and myelodysplastic syndrome (46%), were included in this study. One hundred fourteen patients (61%) were in complete remission at transplantation. Most recipients (73%) were allografted from an adult unrelated donor (URD) and 37 (20%)