Cyclosporine Dose Intensity and Risk of Acute Graft-versus-Host Disease: Trough versus Area under the Curve

Malard et al. [1] reported their observation of an inverse correlation between cyclosporine (CsA) concentrations within the first 2 weeks after hematopoietic stem cell transplantation (HSCT) and the severity of acute graft-versus-host disease (aGVHD). CsA was given first as a continuous i.v. infusion and then orally in patients able to receive oral medication. CsA concentrations are referred to as “trough” concentrations, with no distinction made with respect to route of administration (continuous i.v. infusion vs oral). The proportions of patients receiving i.v. and oral doses each week after HSCT are not stated.

When doses are given on an intermittent schedule, trough drug concentrations are obtained at the end of a dosing interval and before administration of the next dose. In contrast, drug concentrations can be determined at any time during a continuous infusion. They can be either steady-state or non–steady-state concentrations, depending on how long the infusion rate is maintained. Ideally, steady-state concentrations, whether drawn at the end of a dosing interval or during a continuous i.v. infusion, are used to describe the relationship between a drug concentration and a clinical endpoint. In any case, drug concentrations obtained during continuous i.v. infusion do not meet the definition of a trough concentration.

In centers where CsA is given by intermittent i.v. infusion, trough whole blood concentrations are used to individualize doses. Similar to the findings of Malard et al., we reported that in 87 children undergoing myeloablative HSCT, higher trough CsA concentrations during the week before engraftment significantly reduced the odds of developing severe aGVHD (univariate analysis, \( P = .0409 \); multivariate analysis adjusted for type of HSCT, \( P = .0454 \) [2]. The majority of the children (84 of 87) received a bone marrow transplant, and the median day of engraftment was day +18 (mean, day +19.2; range, day +11 to day +35). Therefore, for many children, the week before engraftment coincided with the second week posttransplantation.

Malard et al. [1] raised the question of whether area under the curve (AUC) rather than trough concentration might be a more effective parameter on which to base CsA dosing. Concentrations determined at steady state in patients receiving continuous CsA i.v. infusion can be used to estimate the AUC. Determination of AUC after intermittent i.v. infusion traditionally requires multiple concentration-time points obtained during the dosing interval. We have developed a limited sampling strategy for determining CsA AUC after a 2-hour CsA

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infusion, and in so doing have observed poor correlation (Spearman’s rho = 0.437; \( P = .032 \)) between the concentration obtained 12 hours after the start of the infusion (trough concentration) and AUC [3,4].

We agree with Malard et al. that CsA concentration is an important predictor of aGVHD, that both the magnitude of the CsA concentration and the time relative to HSCT when it is achieved are important in this regard, and that the usefulness of CsA AUC as a predictor of aGVHD should be explored. However, the median weekly CsA concentrations for the first month after HSCT presented by Malard et al. appear to represent a mix of steady-state and non–steady-state concentrations obtained during continuous CsA i.v. infusions and trough concentrations obtained during oral dosing. Thus, it is not possible to fully appreciate the target CsA concentrations proposed by these investigators or their impact on aGVHD severity.

REFERENCES