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Comparison of the effect of different methods of cyclosporine infusion on transplant-related outcomes in allogeneic transplant recipients

Dear editor,

We read with great interest the article entitled "Comparison of continuous versus intermittent infusion cyclosporine and impact on transplant related outcomes in allogeneic transplant recipients" by Engle et al.[1] They retrospectively compared outcomes of patients who received cyclosporine (CsA) via continuous infusion (CIVI) with those who received the medication via twice daily infusion (TDI). They found no significant difference between the two groups neither in terms of the incidence of graft versus host disease (GVHD) nor the overall survival (OS). However, relapse was significantly higher in patients who received CIVI.[1] The findings are clinically important in the setting of hematopoietic stem cell transplantation (HSCT), where there is a high prevalence of GVHD[2] that is associated with non-relapse mortality (NRM).[3] Considering the remarkable role of CsA for GVHD prophylaxis, evaluating the outcomes of different methods of administration is noteworthy. In our opinion, the importance of this issue deserves discussing several points regarding the article.

Engle et al. mentioned that in their center, the administration of CsA to patients intolerant to TDI was switched to CIVI. They also noted that the intolerance often presented with headache, hyperbilirubinemia, or flushing. It was quite informative for the audience to know the literature behind the attribution of these adverse effects to the TDI of CsA. Since distinguishing adverse effects such as hyperbilirubinemia due to CsA from that caused by other medications such as methotrexate or the conditioning regimen is not easy.[4,5] Additionally, previous reports did not show a significant difference in the incidence of hyperbilirubinemia between patients who received CsA, TDI as compared with CIVI.[6]

In the study, patients who received CsA via continuous infusion for at least 48 h during hospitalization for HSCT were eligible to enter the CIVI group. While patients in the TDI group received the whole course of intravenous CsA twice daily before switching to oral medication. Based on the results, patients in the CIVI group received CsA for a median of 9 (ranged from 3 to 32) days that started at a median of 1 (range, –2 to +36) day following the transplantation. Considering these heterogeneities in the duration and starting point of CIVI, putting these patients together in a group, is a considerable limitation which may make it difficult to interpret the results. It seems that attributing a difference in the relapse rate between the groups to the method of administration over a short and diverse period (such as only for 3 days) is not completely appropriate. Additionally, a similar comparison between the CsA methods of administration was conducted in a pediatric population by Umeda et al. On the contrary, patients in each group received only one method of intravenous administration before switching to oral therapy that made the study patients more homogeneous.[6]

Due to the complex and multifactorial nature of GVHD following allogeneic HSCT, Engle et al. investigated the role of the CsA administration method with adjustments for factors such as donor type, conditioning regimen, patients' age, and disease risk index. However, based on the literature, other factors such as performance score, cytomegalovirus (CMV) seropositivity,[2] and total body irradiation[7] were shown to have a significant impact on the incidence of acute GVHD. Similarly, for chronic GVHD factors such as the development of acute GVHD, infusion of donor lymphocytes,[8] grafting with mobilized blood cells, female donors for male recipients, and older donor age[7] were previously demonstrated to influence the occurrence. Thus, it seems that the frequency of these items in groups might have possibly affected the results and worth to be pointed among the limitations of the study.

Additionally, previous studies have found that more than half of the patients had poor medication adherence following allogeneic HSCT.[9] Moreover, the association between immunosuppressive medication non-adherence with clinical consequences such as chronic GVHD was demonstrated.[10] This point particularly emphasizes on the role of factors other than those evaluated in the multiple regression analysis.

Engle et al. found a higher relapse rate in patients who received CIVI versus those who received TDI of CsA when adjusted it for parameters such as donor type, patients' age, conditioning regimen, and disease

risk index. However, previous investigators have identified a significant role of factors such as high WBC count, time to complete remission, blasts at day 15, extramedullary disease, quantifiable levels of minimal residual disease,[11] CMV reactivation, and development of chronic GVHD[12] in relapse following allogeneic HSCT in patients with acute myeloid leukemia (AML). Here we mentioned parameters significant for AML since these patients were the major group that constituted the study population.

In their study, Engle et al. compared NRM between the two groups by considering similar parameters as those noted in the assessment of relapse in the multiple regression analysis. It seems that in this analysis the role of underlying diseases and comorbidities were ignored despite their well-established role in NRM.[13] Several tools have been developed and utilized to predict NRM in HSCT patients[14] that could be used by the researchers.

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