Neurological Complications after Allogeneic Transplantation – Can We Do Better?

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Editorial comment on the paper by Peng Ke et al. Central Nervous System Complications after Allogeneic Hematopoietic Stem Cell Transplantation in Children. Acta Haematol 2019;142:217–223

Neurological complications remain a devastating and feared complication after hematopoietic cell transplantation, and a significant source of morbidity and mortality. The pediatric population represents an especially vulnerable group for whom long-term consequences are of particular concern.

In this issue of *Acta Haematologica*, Ke et al. [1] report the results of a retrospective study of central nervous system complications amongst recipients of 153 consecutive cases of allogeneic stem cell transplantation at a single institution in China. Similar to previous reports, the authors found that central nervous system (CNS) complications were common and usually occur within the first 100 days after transplantation. The most common events were calcineurin inhibitor-associated neurotoxicity, frequently resulting in seizures. Less common but more serious events were cerebrovascular accidents, infections, metabolic encephalopathy, and post-transplant lymphoproliferative disorder. Significantly, the development of neurologic complications portended a poorer prognosis, with increased non-relapsed mortality, decreased progression-free survival, and decreased overall survival amongst patients who developed CNS complications compared with those who did not. These results are in line with previous reports in both pediatric and adult populations [2–5].

A major objective of retrospective studies such as these is to identify risk factors, so as to inform practice and suggest possible interventions to reduce the risk. In their multivariate analysis, Ke et al. [1] identified two risk factors for the developments of CNS complications – longer time from diagnosis to transplant (>4.8 months), and the development of acute graft-versus-host disease (GvHD) grade III–IV. The former is novel, whilst the latter has been previously reported [2, 4, 6]. The precise mechanism by which severe acute GvHD predisposes to CNS complications remains unclear but likely is multifactorial, including critical illness, organ dysfunction, variable absorption and pharmacokinetic effects on drug levels (especially calcineurin inhibitors), and the need for increased immunosuppression. Time from diagnosis to transplant has not been assessed in previous studies of this type. The authors suggest that this finding may be related to the generally adverse outcomes associated with longer time from diagnosis to transplant. Likely, these patients are more heavily pre-treated. Notably, poor disease risk status and prior HiDAC exposure were included as variables in the analysis but not independently associated with CNS risk. In a recent study in adults, apart from severe acute GvHD, the investigators identified age and prolonged thrombocytopenia as risk factors [4]. Thus, a common theme that has emerged is that CNS complica-

tions tend to occur in patients who are experiencing a complex post-transplant course along with other life-threatening complications.

Unfortunately, the risk factors for CNS complications that have been identified in this and prior studies are not directly modifiable prospectively in planning for transplant, such as conditioning, donor selection or GvHD prophylaxis. Thus, the pathway to reducing the risk and improving outcomes remains uncertain. The current study would suggest that moving to transplant as early as feasible may reduce the risk. However, there are many other factors that play into the timing of transplant, most importantly disease status and donor availability. Reducing the risk of CNS complications may be another benefit of moving to transplant quickly. Similarly, reducing the risk of severe acute GvHD has been a primary goal of research towards improved prophylaxis regimens, independent of the effect on the risk of CNS complications. Notably, all patients in the current study received calcineurin inhibitor-based GvHD prophylaxis. As many CNS complications are related to calcineurin inhibitor toxicity, further study may be investigating novel GVHD

prophylaxis regimens. No association was found between serum levels of calcineurin levels and toxicity, meaning that the rationale for dose-adjustment on this basis would be weak.

The paper by Ke et al. [1] makes an important contribution to the literature in this area, which is relatively sparse in the modern era of transplantation. Future studies should focus on prospective collection of data to ensure accurate ascertainment, standardization of definitions, and multi-institutional collaborations to increase statistical power to detect novel risk factors. In the absence of modifiable risk factors at this point in time, the lesson learned is that reduction in the risk of CNS complication is likely to be gradual and results from improvements in supportive care, GvHD prophylaxis, and infection prevention.

Disclosure Statement

The authors declare that they have no conflicts of interest to disclose.

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