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The Doorstep to the Temple of Wisdom

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"The doorstep to the temple of wisdom is knowledge of our own ignorance." Benjamin Franklin.

In this issue, Pidala and colleagues report the appalling state of ignorance and confusion regarding withdraw of immunosuppression (IS) after allogeneic hematopoietic stem cell transplantation (allo HCT) [1]. The authors document marked variation practice (even within the same transplant group), high estimates of graft-vs-host disease (GVHD) emerging in the setting of IS taper, and limited confidence of transplant physicians in their therapeutic decisions. The egress from the temple of stem cell transplant is indeed a jumbled muddle.

The investigators surveyed the American Society Blood and Marrow Transplantation members using a series of clinical vignettes to explore IS management after allo HCT. Unfortunately, only 21% of physician members participated, which does add a note of concern over the validity of the results. Even with this caveat, the results are alarming. For example, 25% indicated that they had no consistent strategy for IS tapering and half said they had no institutional guidelines for IS tapering. There was marked variation among respondents in the taper schedule both in terms of timing and drug dose reduction even in the base case of an uncomplicated HLA identical sibling HCT. As the investigators added complexity to the base case (use of peripheral blood, unrelated donor graft, relapse post transplant, and so forth), the variations and uncertainty increased. Moreover, the respondents estimated that the IS approach they used was likely to result in recurrent acute GVHD (aGVHD) and/or chronic GVHD (cGVHD) in many patients. A total of 41% reported that their current strategy for IS management post-HCT is not adequate, and 26% admitted that they are either uncomfortable or very uncomfortable with making decisions in the management of IS post-HCT.

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What happened to create this muddle of uncertainty? There are multiple factors. First, transplantation has become more diverse. It has gone from 2 basic transplant types (autologous or identical sibling allogeneic) to almost endless combinations of donor types and stem cell sources. Results from clinical trials are often being applied to patients quite different from the original study group. More concerning, these trials were designed to look at engraftment and GVHD prophylaxis, not at effective IS tapering. Although some do report rates of cGVHD, none truly report the burden of GVHD occurring on taper or how many patients required reinstitution of IS. Thus, transplant physicians must make their best guess how to adapt the published regimens to their diverse transplant types. Second, the patient population has also changed, expanding to include older patients and patients with multiple medical illnesses, with marginal organ reserves. This group of patients has less immunologic plasticity and tolerance induction is likely more difficult. The growth of cord blood transplants has introduced a group with the potential for greater immunologic plasticity. Strikingly, the basic practice of transplantation in many ways has not changed. Care of a patient receiving a transplant is usually transferred to a transplant center for a limited period of time. This care model has long impeded the study and care of patients with cGVHD. It certainly contributes to the lack of research into withdraw of IS. Finally, the few trials of prolonged IS in an attempt to reduce the rates of recurrent aGVHD and cGVHD have produced mixed results with no clear indication that longer standard IS is better [2]. Likewise, attempts to prevent cGVHD using immunomodulatory agents have not proven successful [3]. Indeed, the recent premature closure of the HOVON 76 trial of Lenalidomide after reduced-intensity allogeneic transplantation highlights that the unanticipated (induction of aGVHD) may occur even with agents that have been well tolerated in other posttransplant situations (relapse or progression of multiple myeloma) [4].

Is the situation then a hopeless muddle? Certainly the Pidala paper [1] shows that transplant physicians are extremely uncomfortable with the current state and that there is a wide variation in how patients are managed. The investigators suggest several possible approaches to improve our current state of ignorance. Retrospective studies could examine successful IS

discontinuation rates according to tapering schedule. Prospective observational studies could record the IS taper and the associated outcomes. They suggest that this data be used to design prospective randomized trial comparing best approaches for tapering and discontinuation of IS. My own belief is that the often competing factors listed above that created the muddle make prospective clinical trials comparing the withdraw strategies identified as the "best" extremely complicated, time consuming, expensive, and may still produce equivocal results. The investigators suggest another path that is more likely to be fruitful. If validated biomarkers of post-HCT immune tolerance can be developed, these could be used to generate a personalized and informed strategy for IS discontinuation after allo HCT. Our understanding of the genes regulating tolerance after transplant has improved significantly in solid organ transplantation. As summarized recently in an excellent review in this journal, the current concept is that tolerant solid organ transplant patients have a state of immune quiescence with reduced expression of costimulation and immune response genes, and upregulation of cell cycle control genes [5]. CD41CD251FoxP31 regulatory T cells and likely natural killer cells also play important roles in tolerance. Unfortunately, not much is known about the corresponding tolerant stem cell transplant patient, but these same techniques should be able to determine the genetic and cellular profile of tolerant patients. Should these markers be validated, this would allow for rationally designed strategies for IS discontinuance. This approach has the multiple benefits. IS manipulation could be focused on the nontolerant patients who have the most to gain from success while sparing the cost and toxicity of IS in that group of patients who have already achieved a tolerant state. These IS manipulations could be directed at the identified defect. This approach would also avoid the difficulty of having to test IS discontinuance in all the diverse combinations of transplant types.

To close with another quote from Benjamin Franklin, "Being ignorant is not so much a shame, as being unwilling to learn." This paper is a call to all that we have much to learn before we are able to optimally manage the final step of the stem cell transplant procedure.

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