

Donor Lymphocyte Infusion: Beauty Is in the Eye of the Beholder

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In this issue of *Biology Of Blood and Marrow Transplantation*, Bar et al. report on a retrospective analysis of the effect of CD3⁺ cell dose in initial donor lymphocyte infusion (DLI) on graft-versus-host disease (GVHD) and overall survival in 225 patients who received DLI for relapsed hematologic malignancy, primarily at the Fred Hutchinson Cancer Research Center [1]. This article is important from several perspectives, on which I will expound. However, the statement that I enjoyed the most, and the primary focus of my commentary, is in the first sentence of the discussion: “DLI is an attractive salvage treatment option for patients with persistent or relapsed hematologic malignancies.” Attractive? Now, this may be the first time I have heard of DLI being described as attractive. I am sure that I will hear from someone with far too much time on his or her hands of other examples of this adjective to describe DLI, but it did make me take pause. Based on our overall clinical experience with DLI, “attractive” is probably one of the last words I personally would use to describe it. I look at DLI more like having to take your best friend to the prom because neither of you has a date, and neither wants to go to the dance alone. Out of all the other options, what do you do? Beauty is a very relative and subjective term, and maybe it really is in the eye of the beholder.

The report by Bar et al. provides wonderful background for placing the “beauty” of DLI into perspective, reading like a review of the history of DLI over the past 23 years. I would actually argue that that this report should be required reading for fellows during their transplantation rotation and an excellent journal club article. It starts out with the obligatory statement that “Allogeneic hematopoietic cell transplantation has the potential to provide long-term survival and even cure in patients with hematologic malignancies,” which is tough to argue considering that I have started approximately one-half of my own publications with the same statement. This is followed by a statement of who reported the first DLI, which is where it really starts to get interesting, given that even this little 3-patient report has been a repeated point of contention over the years [2,3]. The article then moves on with the “Patients and Methods” section to describe the 225 patients with a broad variety of hematologic malignancies who were treated over an 18-year

period, and then to how specifically DLI was used: with and without chemotherapy or radiation, with adjuvant cytokines (eg, IFN, IL-2), use of steady-state or “mobilized” DLI, chimerism status and presence or absence of GVHD at the time of DLI, and the use of immunosuppression to prevent GVHD. Sound familiar? This is not a criticism—these are extremely relevant biologic and clinical issues that investigators have attempted to address over the past 20 years [4–7].

The authors are self-deprecating when describing the heterogeneity of their patient populations and treatment approaches as a limitation of their study. However, I look at this heterogeneity as a strength, placing the use of DLI in a compact historical framework by a group of investigators who have been at the forefront of translational and clinical transplantation research since its inception. Possibly the most informative (and somewhat comforting) aspect of this report is that the authors’ results are very similar to what has been previously reported and to general perceptions in the transplantation community [8,9]. Consistent with previous observations, Bar et al. found that CD3⁺ dose was correlated with the risk of GVHD, and that higher CD3⁺ doses did not decrease the risk of recurrence after successful DLI or improve overall survival. At the same time, the results are very disappointing relative to the lack of progress in DLI over the last 25 years. The disease for which DLI has the best results, chronic myelogenous leukemia, is today a relatively rare indication for transplantation. We are still unsure as to exactly when, how often, how much, precisely what, and with what we should use DLI. Relative to when, there are no established methods or guidelines for monitoring for disease recurrence after transplantation, with the possible exception of chronic myelogenous leukemia. Bar et al. addressed DLI dose, but the optimal starting dose, whether the doses should be escalated, and if so, how often remain unclear. Maybe we should be giving relatively small (<1 × 10⁶ CD3⁺ cells/kg) on a more frequent (weekly?) basis. Other, possibly even more important questions involve product content and the need for cyto-reduction to achieve a minimal residual disease state and immunodepletion for creation of immunologic “space” [10]. The correlation of success of DLI with minimal residual disease is well established, and it is difficult to expect DLI to be successful in the context of competing for homeostatic and stimulatory cytokines in an immunologically competent host with potentially inhibitory features (eg, T regulatory cells). Relative to content, should they specifically be just CD3⁺ cells or subsets, natural killer cells, or some combination?

Finally, should we just accept it as fact that no matter what we attempt, the results with DLI will end up being the same? It is my strong belief this is the not case; many of these questions have been only partially addressed in an adequate manner, and there are several new modalities, such as chimeric antigen receptors, that may enhance the efficacy of DLI and merit further investigation in the allogeneic

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transplantation setting [11,12]. The key element is the design and implementation of such studies in multi-institutional settings, which was one the major recommendations from the National Cancer Institute's First International Workshop on the Biology, Prevention, and Treatment of Relapse after Allogeneic Hematopoietic Stem Cell Transplantation. Thus is the only way that we are going to determine the optimal use of DLI and to move the field forward [13].

So, as we step back and look across the dance floor, do we really find our date, DLI, attractive? Maybe, if viewed within the context of our other options for recurrent disease after allogeneic hematopoietic cell transplantation. However, I would argue that maybe it is time for the transplantation community to go the ophthalmologist to get our eyes examined.

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