Correspondence

To the editor:

Donor lymphocyte infusions after reduced intensity conditioning allogeneic transplantation: what we need to know

Recently in Blood there were 2 papers that increased our knowledge about donor lymphocyte infusions (DLIs) given after reduced intensity conditioning transplantation.1,2 We published a United Kingdom national study in 81 similar patients 19 months ago.3 This study had a number of limitations mainly because there were multiple different conditioning regimens and the reasons for giving DLIs varied from patient to patient. In conclusion, we suggested that there should be prospective randomized studies to address the major questions. Both of the new published studies have the advantage of uniform conditioning regimens and more complete multilineage chimerism data, but many questions remain.

A recent example perhaps best illustrates the gaps in our knowledge. A colleague contacted us about an adolescent patient with acute myeloid leukemia who received a nonmyeloablative unrelated donor transplant, having relapsed after the first full intensity transplant from the same donor. At a few months after transplantation, she had only 70% to 85% donor chimerism in T cells and myeloid cells. Given that the patient was at such high risk of relapse, an interventional strategy seemed justified, but it was hard to advise about the need for DLI and the chance of conversion to full donor chimerism, the starting dose of T cells, the chance of lethal acute or chronic graft-versus-host disease (GVHD), and the likelihood of reducing relapse risk with DLI.

First, is it necessary to convert a state of stable mixed chimerism to full donor chimerism in the absence of measurable disease? While intuitively the answer is yes, particularly in cases considered to be at high risk of relapse, the recent studies do not provide data regarding the natural history of stable mixed chimerism in the absence of DLIs.1-3 Mixed chimerism can be stable and can be associated with GVHD and a graft-versus-malignancy (GVM) effect.4 In some studies1,3 there does appear to be an association between disease response and conversion to full donor chimerism following DLI, but this is not a universal finding.2,4 These studies also demonstrate that conversion to complete donor chimerism following DLI cannot be guaranteed, occurring in 34% to 82% of patients.1-3 This question becomes more critical in the unrelated donor setting where the incidence of GVHD following DLI may be higher2 and lower starting doses may be required.

If we believe that dose escalation of DLI is the optimal strategy, when should it commence and at what starting dose? The University College Hospital (UCH) study2 gave fixed escalating doses of T cells to recipients at 3-month intervals commencing 6 months following transplantation. This study provided valuable data about DLI-associated toxicity at fixed intervals after transplantation. The Seattle consortium1 using a nonmyeloablative regimen gave DLIs mainly for persistent or relapsed disease (48 of 53 patients). However, there was no prescribed dose of T cells given, and the starting dose was 1 log greater than in the UCH study. The toxicity of DLIs in the sibling setting appears acceptable, with acute GVHD II to IV occurring in 17% to 33% and transient graft hypoplasia, in 0% to 25% of patients.1,3 Of note, none of 23 patients receiving 1 × 106 T cells/kg from a sibling donor at a median of 254 days after transplantation developed acute GVHD.3 However, this may not be the case with unrelated donors, where acute GVHD occurred in 60% of patients at a similar dose. In addition, largely as a consequence of small patient numbers, none of these studies was able to show a clear association between either initial cell dose or timing after transplantation and the incidence of GVHD. Another major unanswered question is when to give the next dose if the first dose is deemed not to have worked. In the Seattle consortium study, the median time before first and second dose was 5.5 weeks, but it ranged from 6 to more than 300 days. When can one safely say that a dose of DLI has not achieved its goal? Very late responses have been seen in a number of patients with chronic myeloid leukemia, and it is possible that some patients receive a second dose of DLI that is not necessary and only adds toxicity. The place of multilineage chimerism in making the decision about the timing of the next dose is also unclear.

A central tenet of reduced intensity allogeneic transplantation has been that the initial transplantation procedure should act as a platform for subsequent allogeneic GVM reactions. The available data seem to support this concept. Even in the absence of adjunctive chemo/radiotherapy disease, responses were seen in 24% to 52% of patients. There are particularly promising responses reported in follicular non-Hodgkin lymphoma, Hodgkin disease, and multiple myeloma, and these responses were associated with the development of GVHD, providing further evidence for a GVM effect in these diseases. It remains a sobering observation, however, that a substantial percentage of these patients ultimately succumbed to subsequent disease progression or the complications of GVHD. Further, disease responses appeared to be less in patients with aggressive leukemias and lymphomas. Considerable further investigation is required to build on these initial observations. Although difficult to launch, large-scale multicenter trials are urgently needed in this important area of transplantation medicine. Distinct protocols may be required depending on the indication for the DLI and the donor relationship, and adjunctive treatment strategies may need to be incorporated for more aggressive diseases. Further studies are needed in pediatric patients, and more data are needed in recipients of unrelated donor transplants. Nonmyeloablative transplantsations are here to stay, but their precise role in patients with different diseases remains to be defined. DLIs will continue to be an important part of this transplantation strategy because mixed chimerism and disease persistence or relapse will continue to be common outcomes of these procedures. Many of the decisions transplant physicians make are not evidence based, but unless we perform systematic prospective studies DLIs will remain among our most uncertain interventions.

David I. Marks, Anne Parker, and Stephen P. Robinson

Correspondence: David I. Marks, Bristol Royal Hospital for Children, Dept of Adult Bone Marrow Transplantation, Upper Maudlin St, Bristol, United Kingdom BS2 8BJ; e-mail: david.marks@ubht.swest.nhs.uk

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To the editor:

HIV Env reduction postreceptor binding: a new target for AIDS treatment?

Markovic et al\(^1\) confirmed recently a role for an oxido-reductase activity, presumed to be that of protein disulfide isomerase (PDI), in the events that follow HIV envelope (Env) binding to cellular receptors. PDI action is thought to enable structural rearrangement of Env that precedes virus-cell fusion. A role for PDI was first reported in the seminal study by Ryser et al\(^2\) in 1994, who observed that the presence of PDI inhibitors during HIV interaction with lymphoid cells impaired infection. We confirmed their study in 2001 and, additionally, addressed the step at which blockade occurs by showing that PDI co-clustered with CD4-enriched regions of the lymphocyte surface is required for HIV/cell fusion.\(^3\) At this stage, the precise mechanism of PDI involvement—reorganization of the Env disulfide network to enable the conformation changes required for fusion or alteration of thiol/disulfide content of other cell surface antigens involved in fusion—was unclear. Recently, in concomitantly accepted manuscripts, we\(^4\) and Ryser et al\(^5\) provided biochemical evidence that reduction of gp120 disulfide bonds by PDI during interaction with the lymphocyte surface was required for fusion. We concluded that 2 disulfide bonds were cleaved in the process.\(^6\) Markovic et al\(^7\) reported that reduction occurs within a multimeric CD4/CXCR4/Env/PDI complex induced by Env binding to the cell surface, which enables gp41 to reach the fusogenic 6-helix bundle conformation.

The data are significant, as they indicate a new area for anti-HIV intervention through development of thiol-interchange inhibitors such as the experimental anti-tumor sulfonylurea analogs\(^8\) and bactracin. Important steps in the process, however, remain unclear: the identification of which disulfides are cleaved and the precise stage in viral entry where cleavage occurs. The latter point is one of debate, as Env reduction has been observed following either CD4\(^1,5\) or CXCR4 interaction.\(^4\) The capacity of the soluble forms of recombinant CD4 to promote Env binding to CXCR4 is more consistent with the PDI-independence of the Env-CXCR4 interaction.

That Env needs conversion by PDI in order to reach its fusogenic conformation highlights the role of cell surface catalysts in the generation of the fusion synapse and shows that the presence of the requisite receptors is not sufficient. In addition to Env, oxido-reduction of CD4 has been observed during HIV/cell fusion.\(^7\) Originally suggested as a requirement for fusion, we suggest, in the light of the data reported above, that CD4 redox change is a consequence of Env reduction and not an independent mechanism. Plausibly, the D2 domain, which does not play an active function in Env binding, acts in a donor/acceptor capacity to enable the gp120 reduction.

In addition to drug development, and as noted in a commentary here by Kornbluth,\(^8\) partially reduced Env may constitute a vaccine candidate capable of eliciting neutralizing antibodies directed against epitopes masked on the native antigen. Encouragingly, if the required antibodies could be induced, the half-life of the fusion intermediate at the cell surface appears sufficient\(^4\) to enable antibody binding to occur.

Emmanuel Fenouillet, Rym Barbouche, and Ian M. Jones
Correspondence: Emmanuel Fenouillet, Department of Biochemistry, CNRS School of Medicine, Blvd Dramard, Marseille, 13015 France; e-mail: fenouillet.e@jean-roche.univ-mrs.fr

References

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