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HEMATOPOIESIS & STEM CELLS

Comment on Kean et al, page 6580

Can we build a better allograft?

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Compelling evidence has been accumulating recently implicating disruption of CXCR4/CXCL12 signaling as a key step in the mobilization of hematopoietic stem and progenitor cells (HSPCs) induced by G-CSF and other agents.[1,2] This knowledge formed the rationale for the clinical development and ultimate FDA approval of a specific CXCR4 antagonist, AMD3100, for the mobilization of HSPCs in patients with non-Hodgkin lymphoma and multiple myeloma when given in combination of G-CSF.[3,4]

In this issue of *Blood*, Kean and colleagues have taken advantage of the knowledge that CXCR4 is also widely expressed on a variety of lymphoid subsets to study the effects of AMD3100 on lymphoid cell mobilization.[5] Using a clinically relevant rhesus macaque model, they compared the composition of multiple cellular subsets mobilized at various time points into the peripheral blood after treatment with G-CSF alone, AMD3100 alone, or the combination. They went on to perform leukapheresis after mobilization and compared the products obtained. Interestingly, the overall number of phenotypically defined conventional $CD4^+$, $CD8^+$, T-effector memory (Tem), T-regulatory (Treg) cells, and plasmacytoid dendritic cells (pDCs) were increased several fold after AMD3100 alone or in combination with G-CSF compared with G-CSF alone. Accordingly, the leukapheresis products obtained also contained greater amounts of these cells. These data corroborate findings from a small clinical trial where a greater number of $CD3^+$ cells were observed in AMD3100-mobilized allografts compared with G-CSF–mobilized products.[6]

Why are these preliminary studies important? For the bone marrow transplantation (BMT) field, they imply that quantitative differences in an allograft product could have functional consequences, possibly influencing the risk of acute or chronic GVHD as well as the pace of immune reconstitution after transplantation. The greater Treg and Tem populations could mitigate the risk of GVHD, while the increased numbers of pDCs could impact GVHD or the risk of viral infection given their putative role in controlling viral replication. The flip side of the coin raises concerns that graft versus malignancy effects could be diminished by these cell populations. Alternatively, those transplanted for nonmalignant indications may benefit overall.

To provide some perspective, over the past decade cytokine mobilized peripheral blood has largely replaced bone marrow as the preferred allograft source for patients with hematologic malignancies undergoing HLA-matched related transplantation-based on studies that collectively demonstrated more rapid hematopoietic reconstitution and better disease control for those with advanced malignancy.[7] Investigators have extrapolated these results to the unrelated donor setting, leading to greater use of mobilized peripheral blood progenitor cell (PBPC) grafts compared with BM from unrelated donors. The results of a recently completed randomized trial conducted by the Blood and Marrow Transplant Clinical Trials network (BMT CTN 0201; NCT#00075816) should be released shortly and will clarify whether this is appropriate. To date, however, overall survival does not appear to be improved with PBPC compared with BM due mainly to a higher risk of chronic GVHD, likely resulting from the greater number of T cells transplanted in these grafts. For patients with aplastic anemia, the results are worse with PBPC than BM because of GVHD.[8,9] Thus, improving the results of PBPC transplants remains an important goal among BMT investigators, but has been difficult to tackle. The studies by Kean et al suggest an alternative strategy: rethinking the way we obtain mobilized peripheral blood allografts.

Like so many interesting early studies, the findings of Kean and colleagues raise more questions than they answer. Given the potential to impact GVHD, what is the best target patient population? A pilot study suggested AMD3100 alone mobilized lower $CD34^+$ cell numbers in allografts compared with G-CSF.[6] Are the quantities of $CD34^+$ cells mobilized by AMD3100 sufficient to ensure rapid and sustained hematopoietic engraftment or would it need to be combined with G-CSF? Alternatively, would lower $CD34^+$ cell doses be sufficient if they possessed better homing capacity based on higher CXCR4 expression compared with G-CSF mobilized $CD34^+$ cells? If combined with G-CSF, how many days of treatment would be optimal? Should only matched sibling donors be targeted or also unrelated volunteers? What are the most appropriate endpoints for such studies, and which study design would be most efficient? Of note, the Center for International Blood and Marrow Research (CIBMTR) Resource for Clinical Investigation in BMT (RCI BMT) is planning a phase 2 study of AMD3100 only to mobilize allografts from HLA-matched related donors of patients with hematologic malignancies. The primary end point of this study will be the quantity of $CD34^+$ cells mobilized with important secondary endpoints including the rates of hematopoietic reconstitution and both acute and chronic GVHD. This multicenter study should shed light on the feasibility of using AMD3100 alone to mobilize donor allografts.

Other interesting possibilities for further study include the capacity of AMD3100 to mobilize lymphoid subsets useful for adoptive cellular therapy (eg, Treg of NK-cell infusions) or to increase the number of cells that could be modified by extracorporeal photopheresis, a method used to treat GVHD.

Other possibilities include combinations with other drugs to treat CXCR4 expressing malignancies (so called chemo-sensitization) and as an adjuvant to prevent the risk of GVHD associated with solid organ transplantation (eg, small bowel).

Above all else, it is important to raise the issue of donor safety. Safety is paramount. Any strategy aiming to change the method by which we obtain a donor allograft must be proven to be safe for donors both in the short and long term. To date, AMD3100 has been well tolerated in donors and acute toxicities greater than grade 2 are rare. Fewer data are available on any long term consequences in normal individuals so just as with G-CSF, this will need to be tracked closely. That said, the studies reported here by Kean et al are important because they suggest that not all allografts are created equal. We may now have the tools available to build a better allograft.

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● ● ● LYMPHOID NEOPLASIA

Comment on Ward et al, page 6610

Finally, a transgenic light chain amyloidosis mouse model

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Ward and colleagues report the first transgenic light chain amyloidosis mouse model in this issue of *Blood* and demonstrate that it can be used to test pharmaceutical candidates.[1]

Light chain amyloidosis results from the misfolding and aggregation of an immunoglobulin light chain usually produced by clonal plasma cells in the bone marrow. Hence, light chain amyloidosis is both a cancer and an amyloid disease and is the most rapidly fatal of the systemic amyloid diseases. Patients with light chain amyloidosis are usually treated with chemotherapy agents to eradicate the plasma cell clone. However, the toxicity of these drugs in the background of proteotoxicity caused by the process of light chain amyloid fibril formation (amyloidogenesis) often limits how much of the chemotherapeutics can be given.[2-5] Several experts have hypothesized that if amyloidogenic light chain secretion and/or light chain amyloidogenesis could be blocked, the associated organ toxicity would be ameliorated, enabling more aggressive and effective chemotherapy regimens to be used.

While transgenic cell and murine models are now available for nearly every human amyloid disease, these have proven elusive for light chain amyloidosis despite significant effort on the part of several laboratories. Light chain amyloidosis mouse models have been hard to generate probably because of the severe cytotoxicity and organ toxicity associated with the process of light chain amyloidogenesis—leading to embryonic lethality. Here, Ward et al report the long-awaited first transgenic murine model of light chain amyloidosis.[1]

The amyloidogenic light chain levels in the 3 lines generated are comparable with nonamyloidogenic light chain levels found in healthy human adults. Because the efficiency and rate of amyloid formation is dependent on the concentration of amyloidogenic light chain, the low plasma concentration of amyloidogenic light chain minimizes amyloidogenesis, which is probably why these mouse lines could be generated. It is envisioned that these mice will be very useful for evaluating proteostasis regulator candidates that selectively lower amyloidogenic light chain secretion without altering proteome secretion in general, including antibody secretion.[6] Moreover, Ward et al showed that all 3 mouse lines produce amyloid in the lumen of the gastric glands of the stomach. The acidic environment of the stomach probably partially unfolds the destabilized light chain, which then forms a conformational intermediate that misassembles, leading to a dysplastic stomach epithelium and dilated glands filled with light chain amyloid. Approximately 20% of the transgenic mice exhibited a neurodegenerative phenotype reflected by a gait disturbance and limb clenching when the mice were picked up by the tail, and these mice demonstrated impaired inclined treadmill performance.

Ward and colleagues beautifully demonstrated that these mice could be used to assess the efficacy of anti–light chain amyloid drug candidates.[1] Transgenic mice 3 to 6 months of age were treated with doxycycline in the drinking water. After 7 months of treatment, 23% of the mice had stomach amyloid detected by Congo red versus 69% of the untreated group. While the mechanism of doxycycline action merits further investigation, what is clear is that this murine model is useful for testing antiamyloid agents.

Like almost all "first transgenic disease models," this is not the ultimate murine model in that amyloidogenic light chain expression is low and amyloidogenicity appears to require the acidity of the gastric gland to occur. However, this model appears to be superior to the nontransgenic mouse models. These include a model introduced by Pepys and colleagues wherein they repeatedly injected human light