marked cardiac dysfunction measured by elevations in the serum biomarkers NT-proBNP and troponin. Grade 3 or 4 toxicity was observed in 54%, which was similar in nature to that observed in other IMiD trials in AL and included fluid retention, infection, atrial fibrillation, and venous thromboembolism.[2] Nevertheless, analogous to the recent trend noted previously by Muchtar et al, no deaths occurred within the initial 100 days of pomalidomide therapy. However, these side effects and the rates of pomalidomide dose reduction (32%) and discontinuation (29%) resulting from adverse events emphasize the challenges in optimizing the treatment of AL and support future trials to explore dose and schedule modifications to improve tolerance.[2] Such efforts might include dose reduction of pomalidomide, as suggested by the authors, dose reduction of dexamethasone, or administration of pomalidomide on days 1 through 21 of a 28-day schedule (as approved for myeloma) rather than continuously; pomalidomide combinations as initial therapy for AL would also be of interest.

Exciting laboratory research also portends well for identifying better prognostic factors and treatment strategies in AL. Fluorescence in situ hybridization cytogenetics, preferential organ tissue trophism according to AL variable region gene selection, relevance of marrow minimal residual disease, and chemical characteristics of specific ALs that predict their predisposition for self-aggregation are subjects of active investigation, and the results may be leveraged in the future to improve management strategies.[9-11] We look forward to the next analysis of the Mayo Clinic or other large AL database to demonstrate that further improvements in outcomes for AL patients have been achieved in the real-world setting.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

REFERENCES

1. Muchtar E, Gertz MA, Kumar SK, et al. Improved outcomes for newly diagnosed AL amyloidosis between 2000 and 2014: cracking the glass ceiling of early death. *Blood*. 2017;129(15):2111-2119.

2. Palladini G, Milani P, Foli A, et al. A phase 2 trial of pomalidomide and dexamethasone rescue treatment in patients with AL amyloidosis. *Blood*. 2017;129(15):2120-2123.

3. Dispenzieri A, Merlini G. Immunoglobulin light chain systemic amyloidosis. *Cancer Treat Res*. 2016;169:273-318.

4. Jelinek T, Kufova Z, Hajek R. Immunomodulatory drugs in AL amyloidosis. *Crit Rev Oncol Hematol*. 2016;99:249-260.

5. Comenzo RL, Gertz MA. Autologous stem cell transplantation for primary systemic amyloidosis. *Blood*. 2002;99(12):4276-4282.

6. Palladini G, Perfetti V, Obici L, et al. Association of melphalan and high-dose dexamethasone is effective and well tolerated in patients with AL (primary) amyloidosis who are ineligible for stem cell transplantation. *Blood*. 2004;103(8):2936-2938.

7. Reece DE, Hegenbart U, Sanchorawala V, et al. Efficacy and safety of once-weekly and twice-weekly bortezomib in patients with relapsed systemic AL amyloidosis: results of a phase 1/2 study. *Blood*. 2011;118(4):865-873.

8. Gertz MA. Immunoglobulin light chain amyloidosis: 2016 update on diagnosis, prognosis, and treatment. *Am J Hematol*. 2016;91(9):947-956.

9. Muchtar E, Dispenzieri A, Kumar SK, et al. Interphase fluorescence in situ hybridization in untreated AL amyloidosis has an independent prognostic impact by abnormality type and treatment category [published online ahead of print 16 December 2016]. *Leukemia*.

10. Kourelis TV, Dasari S, Theis JD, et al. Clarifying immunoglobulin gene usage in systemic and localized immunoglobulin light-chain amyloidosis by mass spectrometry. *Blood*. 2017;129(3):299-306.

11. Muchtar E, Jevremovic D, Dispenzieri A, et al. The prognostic value of multiparametric flow cytometry in AL amyloidosis at diagnosis and at the end of first-line treatment. *Blood*. 2017;129(1):82-87.

DOI 10.1182/blood-2017-02-765560

HEMATOPOIESIS AND STEM CELLS

Comment on Shimoto et al, page 2124

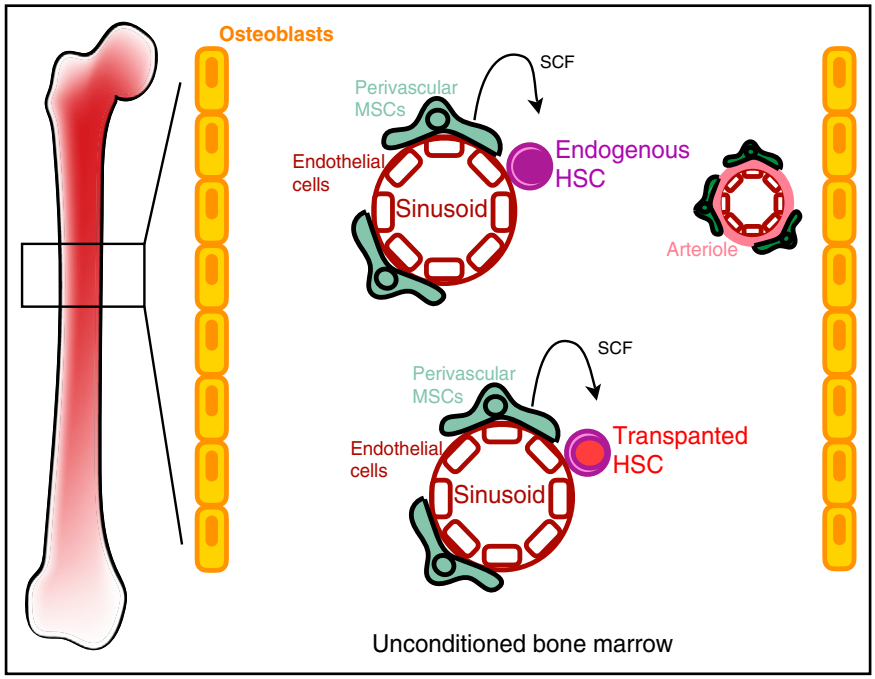
HSC niche: ample room for every guest stem cell

Lei Ding COLUMBIA UNIVERSITY MEDICAL CENTER

It has long been thought that nearly all bone marrow niches are occupied by hematopoietic stem cells (HSCs). In this issue of *Blood*, Shimoto et al show that the bone marrow contains more habitable niches for HSCs.[1]

HSCs reside in specialized bone marrow microenvironmental niches and generate all lineages of blood and immune cells throughout life. HSC-based transplantation has been widely used in clinics to treat a variety of hematological malignancies. Inefficient HSC engraftment has been a major roadblock limiting the success of transplantation. Among several engraftment-limiting factors, the availability of bone marrow space for HSCs has been a focus of research in the field. The necessity of wiping off endogenous HSCs is illustrated by studies demonstrating that virtually no engraftment will be achieved if syngeneic recipients receive no myeloablative conditioning.[2] One explanation of these data is that there are limited numbers of niches for HSCs, such that transplanted HSCs can only effectively engraft after these niches are emptied. Several lines of evidence support this model. For example, it has been suggested that most HSC niches are occupied and that only about 0.1% to 1.0% of niches are thought to be open for engraftment at any given time in unconditioned recipients.[3,4] Other studies have shown that transplanting large numbers of unfractionated bone marrow cells led to high levels of engraftment in unconditioned mice.[5,6] These data suggest that chimerism levels after transplantation are determined by the ratio of exogenous to endogenous stem cells, suggesting a model in which exogenous HSCs can compete with endogenous HSCs to engraft bone marrow without the niches being empty.[5] Certain accessory cells in the bone marrow transplant have been suggested to account for the experimental differences between purified HSCs and bone marrow cell transplantation.[7] Regardless of the model of how exogenous HSCs engraft, it is thought that essentially all niches or spaces within bone marrow are occupied by endogenous HSCs in unconditioned mice.

Now, Shimoto et al challenge this view by showing that donor HSCs can significantly engraft in the bone marrow and occupy distinct perivascular niches of unconditioned mice without competing out endogenous HSCs (see



Many facultative niches are available for HSCs in unconditioned bone marrow. Upon transplantation, exogenous HSCs will engraft these niches without competing out endogenous HSCs. These niches appear to be identical to endogenous niches in terms of cellular composition and signaling (dependence on stem cell factor [SCF]). The empty niches could be harnessed to improve HSC engraftment for safer transplantation.

figure). Previous work in the field, including some from the author's group, had identified a bone marrow sinusoidal perivascular niche for HSCs, where Cxcl12^{+}Lepr^{+} perivascular stromal cells are a key component.[8] These cells are more frequent than HSCs in the bone marrow, raising the possibility that there are more niches than HSCs in vivo. The authors address this issue by investigating whether HSCs can engraft the bone marrow of unconditioned mice. To reliably detect engraftment in the background of endogenous HSCs, a large number of donor HSCs is needed. However, the rarity of HSCs in the bone marrow has made it technically challenging. The authors undertook a heroic effort by sorting a large number of HSCs from 100 to 200 donor mice. By transplanting a very large number of HSCs (up to 390% of endogenous HSCs) into unconditioned mice, the authors had the opportunity to measure a significant number of donor-derived HSCs. Surprisingly, they found that these transplanted donor HSCs did not outcompete endogenous HSCs. Rather, they engrafted distinct niches and differentiated to mature blood cells. As a result, total HSC numbers (endogenous plus transplanted) were higher. By marking HSCs with a pulse of histone H2B-GFP fusion protein expression (but not their downstream hematopoietic progenies, because of signal dilution after each cell division) and leukocyte CD45 marker (to distinguish donor vs recipient type), the authors assessed the in vivo localization of engrafted and endogenous HSCs. Just like their endogenous counterparts, the transplanted HSCs scattered singly throughout the bone marrow and were in close contact with sinusoidal perivascular stromal cells, but not arterioles. In addition to being physically localized to the perivascular niches, transplanted HSCs were dependent on SCF secreted by the Lepr^{+} perivascular stromal cells. Interestingly, the expanded HSC compartment was not carried over to downstream granulocyte and monocyte progenitors, suggesting that the niches for these myeloid progenitors are saturated during homeostasis.

Altogether, these data convincingly show that there are a large number of empty HSC niches at least capable of supporting HSCs at numbers similar to endogenous HSCs in the bone marrow. This represents an important conceptual step forward in our understanding of the bone marrow microenvironment that supports HSCs. This research will spark more investigation into the question of what the nature of the niche is. Why is there an excess of niches? Why are these empty niches not occupied by endogenous HSCs? Are HSCs constantly moving among these niches? What are the in vivo limits that constrain the number of HSCs in the bone marrow? Answers to these questions will provide important insights on how HSCs are maintained in vivo.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

REFERENCES

1. Shimoto M, Sugiyama T, Nagasawa T. Numerous niches for hematopoietic stem cells remain empty during homeostasis. *Blood*. 2017;129(15):2124-2131.

2. Tomita Y, Sachs DH, Sykes M. Myelosuppressive conditioning is required to achieve engraftment of pluripotent stem cells contained in moderate doses of syngeneic bone marrow. *Blood*. 1994;83(4):939-948.

3. Bhattacharya D, Rossi DJ, Bryder D, Weissman IL. Purified hematopoietic stem cell engraftment of rare niches corrects severe lymphoid deficiencies without host conditioning. *J Exp Med*. 2006;203(1):73-85.

4. Czechowicz A, Kraft D, Weissman IL, Bhattacharya D. Efficient transplantation via antibody-based clearance of hematopoietic stem cell niches. *Science*. 2007;318(5854):1296-1299.

5. Westerhuis G, van Pel M, Toes RE, Staal FJ, Fibbe WE. Chimerism levels after stem cell transplantation are primarily determined by the ratio of donor to host stem cells. *Blood*. 2011;117(16):4400-4401.

6. Brecher G, Ansell JD, Micklem HS, Tjio JH, Cronkite EP. Special proliferative sites are not needed for seeding and proliferation of transfused bone marrow cells in normal syngeneic mice. *Proc Natl Acad Sci USA*. 1982;79(16):5085-5087.

7. Nilsson SK, Dooner MS, Tiarks CY, Weier HU, Quesenberry PJ. Potential and distribution of transplanted hematopoietic stem cells in a nonablated mouse model. *Blood*. 1997;89(11):4013-4020.

8. Morrison SJ, Scadden DT. The bone marrow niche for haematopoietic stem cells. *Nature*. 2014;505(7483):327-334.

DOI 10.1182/blood-2017-02-765586