Leukemia suppressing normal bone marrow: how long does it last?

Mauricio Nicolas Ferrao Blanco,[1] Mirjam Belderbos,[1] Hermann Josef Vormoor[1,2]

[1]Princess Máxima Center for Pediatric Oncology and [2]University Medical Center Utrecht, Utrecht, The Netherlands

Correspondence: H.J. Vormoor
h.vormoor@prinsesmaximacentrum.nl

Received: March 18, 2023.
Accepted: March 24, 2023.
Early view: April 6, 2023.

https://doi.org/10.3324/haematol.2023.282955

Patients with newly diagnosed leukemia often present with signs and symptoms of bone marrow (BM) failure rather than with symptoms caused by proliferation of the leukemia itself: e.g., paleness, tiredness and lack of energy due to anemia; pro-longed or severe infections due to neutropenia; and petechial rash and nose bleeds due to thrombocytopenia. BM failure is a relatively late event during leukemia development. It is thought to be either a direct, cyto-/chemokine-mediated effect of the leukemic cells or an indirect effect via re-modeling of the BM environment. Either or both lead to suppression of normal BM function. Many studies have investigated the interaction of normal hematopoietic stem and leukemia cells with their BM niche. It has been shown that different types of leukemia affect differentiation and function of various cells in the BM, including bone progenitor cells, endothelial cells, nerve fibers and myofibroblasts,[1] leading to a loss of support of normal hematopoiesis.

In this issue of *Haematologica*, Jensen *et al*. investigated the effect of B-lineage acute lymphoblastic leukemia (B-ALL) on residual normal hematopoiesis.[2] They use a spontaneous murine leukemia model with heterozygote deletions of *Pax5* and *Ebf1*, and study the effect of the leukemia on normal hematopoiesis by transplanting leukemic blasts onto wild-type mice. Interestingly, and in contrast to what one might expect as a consequence of modulation of the BM niche, the most immature $Lin^-KIT^+SCA1^+$ (LSK) and $CD150^+$ LSK stem-like compartment persists, while more mature, lineage-restricted progenitors disappear from the leukemic marrow. A similar observation was made in 19 human patients with B-ALL in which the frequency of non-leukemic $CD19^-CD34^+CD38lo^{w/-}$ putative stem-like cells was comparable to normal controls. Most intriguingly, the authors describe a lasting effect of the leukemia on the reconstitution potential of these murine stem cells after primary and secondary transplantation. Secondary mice transplanted with "leukemia-exposed" hematopoietic stem cells showed lower levels of reconstitution. The "leukemia-exposed" $CD150^+$ LSK cells displayed an expression profile suggestive of mitochondrial dysfunction, with fluorescent dye tracking confirming a reduced mitochondrial membrane potential in this residual stem cell population. Impaired mitochondrial function is a hallmark of cellular aging,[3] and these data are, therefore, suggestive of premature aging of "leukemia-exposed" hematopoietic stem cells.

There are two key questions that arise from this work.

1) What is the mechanism by which the leukemia imposes such a long-lasting effect on the repopulation potential of normal stem cells leading to mitochondrial dysfunction and premature aging of the hematopoietic compartment?

Mitochondrial dysfunction is a common feature of many types of cancer, including leukemia. To meet their high energetic demands, leukemia cells rely on mitochondrial oxidative metabolism. Pharmacologic inhibition of oxidative metabolism has been demonstrated to inhibit leukemia cell growth and to increase sensitivity to chemotherapy, both *in vitro* and *in vivo*.[4,5] Intriguingly, the damaging effects of chemotherapy can, at least in part, be rescued by transfer of mitochondria between leukemia cells and their surrounding BM stroma.[6,7] Similarly, BM stromal cells were found to transfer mitochondria to healthy hematopoietic stem cells as a means to promote their capacity to respond to proliferative stress.[8] Although direct exchange of mitochondria between leukemia cells and healthy hematopoietic stem/progenitor cells has not been demonstrated, it is interesting to think about whether or how mitochondrial transfer could account for the findings by Jensen *et al*. Alternatively, one could envision a tripartite exchange in which BM niche cells are the intermediate party, transferring mitochondria from leukemia cells towards the resident normal hematopoietic stem cells (and potentially, vice versa). Although a role for mitochondrial exchange remains speculative, if confirmed, it could provide the route to develop new therapeutic interventions to protect the healthy hemato-

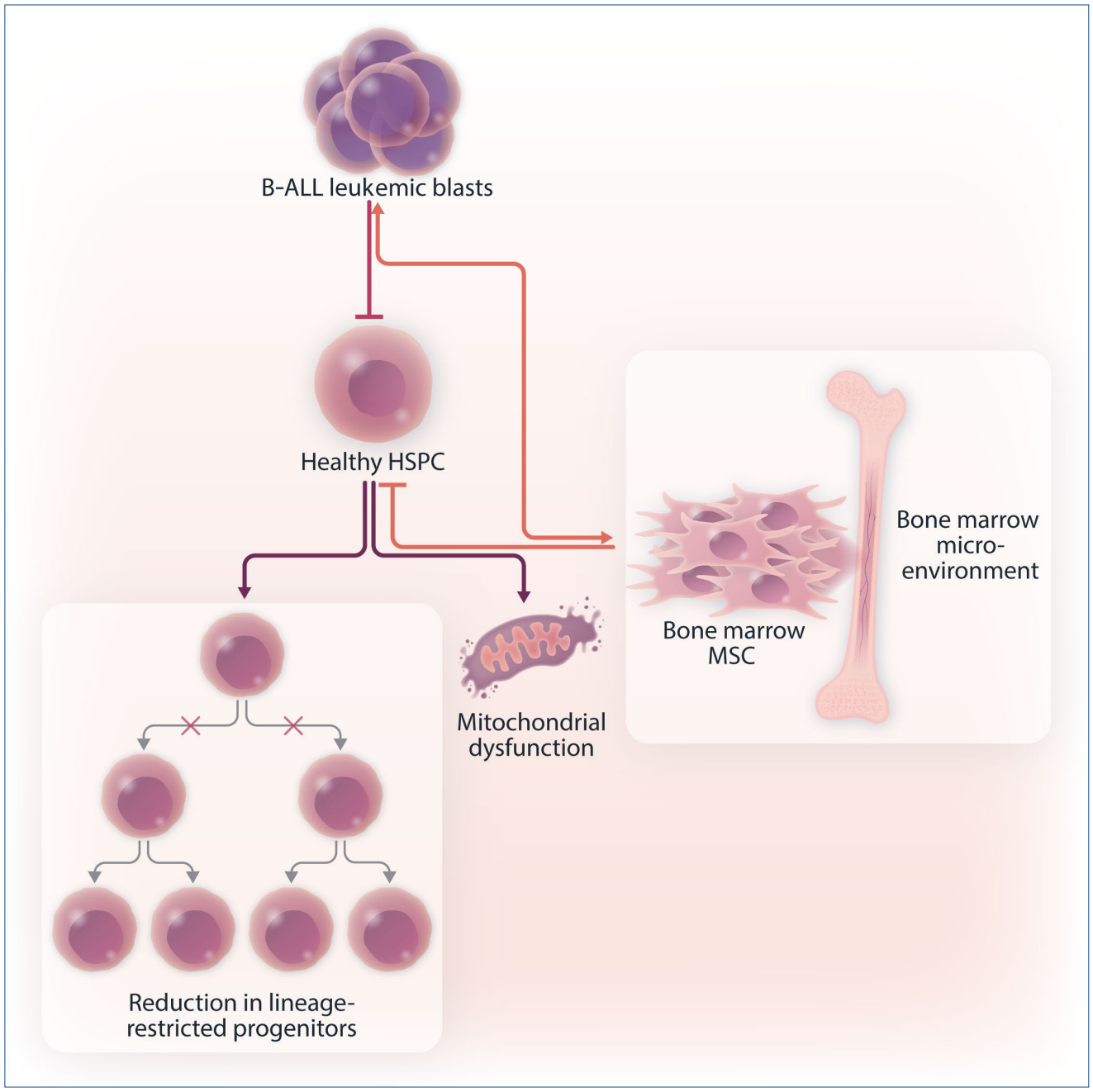

Figure 1. Leukemia-induced mitochondrial dysfunction in hematopoietic stem and progenitor cells limits their ability for long-term reconstitution, recapitulating aging. B-cell acute lymphoblastic leukemia (B-ALL)-exposed hematopoietic stem and progenitor cells (HSPC) produce reduced numbers of lineage-restricted progenitor cells, and exhibit mitochondrial dysfunction. Some of these effects may be indirectly mediated, by cross-talk of B-ALL blasts, bone marrow mesenchymal stromal cells (MSC) and the healthy HSPC compartment. Created with BioRender (BioRender.com).

poietic stem cell compartment from leukemia-mediated suppression.

2) Does this long-lasting effect of the leukemia on normal hematopoietic stem cells also occur in human patients? Or is the described effect on stem cells unique to this mouse model?

Clonal hematopoiesis has been studied in long-term survivors of pediatric cancer.[9] There is a significant increase in clonal hematopoiesis in childhood cancer survivors; however, this is mainly thought to be therapy-related rather than there being evidence for a leukemia-mediated accelerated aging of normal hematopoietic stem cells. Late BM failure is not usually regarded as a typical late effect after ALL.[10] However, data on clonal hematopoiesis in survivors of childhood ALL, particularly in very long-term survivors, are scarce. This interesting observation suggests that aging of the hematopoietic system in our patients warrants further attention, and future prospective studies are needed to look at BM function in long-term survivors.

Disclosures

No conflicts of interest to disclose.

Contributions

MF, MB and JV wrote the manuscript. MF designed the figure.

References

1. Pinho S, Frenette PS. Haematopoietic stem cell activity and interactions with the niche. Nat Rev Mol Cell Biol. 2019;20(5):303-320.
2. Jensen CT, Åhsberg J, Tingvall-Gustafsson J, et al. B-lineage acute lymphoblastic leukemia causes cell autonomous defects in long-term hematopoietic stem cell function. Haematologica. 2023;108(11):3175-3180.
3. Kauppila TES, Kauppila JHK, Larsson NG. Mammalian mitochondria and aging: an update. Cell Metab. 2017;25(1):57-71.
4. Saito K, Zhang Q, Yang H, et al. Exogenous mitochondrial transfer and endogenous mitochondrial fission facilitate AML resistance to OxPhos inhibition. Blood Adv. 2021;5(20):4233-4255.
5. Bosc C, Saland E, Bousard A, et al. Mitochondrial inhibitors

circumvent adaptive resistance to venetoclax and cytarabine combination therapy in acute myeloid leukemia. Nat Cancer. 2021;2(11):1204-1223.
6. Griessinger E, Moschoi R, Biondani G, Peyron JF. Mitochondrial transfer in the leukemia microenvironment. Trends Cancer. 2017;3(12):828-839.
7. Burt R, Dey A, Aref S, et al. Activated stromal cells transfer mitochondria to rescue acute lymphoblastic leukemia cells from oxidative stress. Blood. 2019;134(17):1415-1429.
8. Mistry JJ, Marlein CR, Moore JA, et al. ROS-mediated PI3K activation drives mitochondrial transfer from stromal cells to hematopoietic stem cells in response to infection. Proc Natl Acad Sci U S A. 2019;116(49):24610-24619.
9. Hagiwara K, Natarajan S, Wang Z, et al. Dynamics of age- versus therapy-related clonal hematopoiesis in long-term survivors of pediatric cancer. Cancer Discov. 2023;13(4):844-857.
10. Dixon SB, Chen Y, Yasui Y, et al. Reduced morbidity and mortality in survivors of childhood acute lymphoblastic leukemia: a report from the Childhood Cancer Survivor Study. J Clin Oncol. 2020;38(29):3418-3429.