haematologica
Journal of the Ferrata Storti Foundation

LIPA-frogging blast phase chronic myeloid leukemia: hopping over resistance with lysosomal targeting

by Miguel Quijada-Álamo, Grace Freed, and Elvin Wagenblast

Received: July 30, 2024.
Accepted: August 9, 2024.

Citation: Miguel Quijada-Álamo, Grace Freed, and Elvin Wagenblast.
LIPA-frogging blast phase chronic myeloid leukemia: hopping over resistance with lysosomal targeting.
Haematologica. 2024 Aug 22. doi: 10.3324/haematol.2024.286140 [Epub ahead of print]

LIPA-frogging blast phase chronic myeloid leukemia: hopping over resistance with lysosomal targeting

Miguel Quijada-Álamo[1], Grace Freed[1] & Elvin Wagenblast[1*].

1. Department of Oncological Sciences, Tisch Cancer Institute, Black Family Stem Cell Institute, Mindich Child Health & Development Institute and Department of Pediatrics, Division of Pediatric Hematology-Oncology, Icahn School of Medicine at Mount Sinai

*Correspondence: elvin.wagenblast@mssm.edu

Correspondence

E. Wagenblast elvin.wagenblast@mssm.edu

Disclosures

No conflicts of interest to disclose.

Contributions

All authors contributed equally.

In this issue of *Haematologica*, Minhajuddin et al.[1] provide a compelling analysis of the combinatorial therapy of venetoclax and tyrosine kinase inhibitors (TKIs) for treating blast phase chronic myeloid leukemia (bpCML). Despite significant improvements in chronic myeloid leukemia (CML) outcomes due to the development of TKIs, a subset of patients still progresses to bpCML, which is associated with dismal prognosis and a median survival of less than one year.[2] The treatment of bpCML remains a significant challenge due to drug resistance of leukemia stem cells (LSCs),[3] requiring the development of new therapeutic strategies that specifically target this resistant population. Preclinical studies have indicated that combining the selective BCL-2 inhibitor venetoclax with TKIs holds promise for both chronic phase and bpCML.[4] Minhajuddin et al. delve into the mechanistic underpinnings of this combinatorial therapy, identifying a key role for lysosomal acid lipase A (LIPA) in the adaptative response of bpCML LSCs and highlighting a new vulnerability of these cells to lysosomal function disruption.[1]

BCL-2 family members are proteins involved in mitochondrial-related apoptosis and have been shown to be critical for the survival of leukemia cells. Indeed, selective inhibition of the anti-apoptotic protein BCL-2 by the FDA-approved compound venetoclax, has emerged as a promising strategy for the treatment of various lymphoid and myeloid leukemias.[5] In CML, BCL-2 levels are elevated compared to normal hematopoietic stem cells and are further increased in bpCML.[6] Since TKI treatment alone often fail to eradicate CML LSCs, combining venetoclax with TKIs could enhance treatment efficacy, particularly in bpCML. Minhajuddin et al. demonstrate that the venetoclax and dasatinib combination effectively targets LSCs in both the Bcr-Abl Nup98-Hoxa9 bpCML mouse model and in primary bpCML cells. This combination therapy led to complete elimination of bpCML cells and, importantly, LSCs exposed to the drug combination were not able to engraft in secondary recipients, indicating the successful eradication of the bpCML LSC compartment. Further, they generated a novel bpCML mouse model harboring T315I Bcr-Abl mutation in combination with Nup98-Hoxa9 translocation and showed enhanced efficacy of

venetoclax in combination with the third-generation TKI ponatinib. This is of particular relevance, since more than 40% of bpCML cases harbor tyrosine-kinase domain mutations in BCR-ABL conferring resistance to earlier-generation TKIs.[7] It would be of special interest in future studies to assess the efficacy of venetoclax in combination with the next-generation TKI asciminib, which has been shown to be active in CML patients after ponatinib or other TKI failure.[8]

Understanding the molecular mechanisms underlying the bpCML LSC-targeting activity of venetoclax and TKI combination therapy is crucial for anticipating potential mechanisms of resistance and identifying new actionable pathways that could be leveraged to enhance therapeutic outcomes. Minhajuddin et al. performed RNA sequencing of bone marrow LSC-sorted populations treated with dasatinib alone or combined with venetoclax, revealing an upregulation of genes involved in lysosomal biology in cells exposed to the combination therapy. Notably, LIPA, an enzyme involved in free fatty acid regulation, was significantly elevated in LSCs treated with both venetoclax and dasatinib, resulting in increased production of several fatty acids such as α-linolenic acid and dihomo-γ-linolenic acid. LIPA overexpression in murine bpCML LSCs or fatty acid media supplementation conferred partial resistance to the combination therapy. Conversely, LIPA knockout in murine bpCML LSCs, LIPA knockdown in primary bpCML cells and inhibition of lysosomal function with bafilomycin increased sensitivity to the treatment. Collectively, these results indicate that LIPA-driven lysosomal and fatty acid pathways contribute to the protective response of bpCML LSCs to venetoclax and TKIs, laying the ground for further exploration of these pathways as potential targets for inhibition in the context of dual BCL-2 and tyrosine kinase inhibition.

The implications of fatty acid metabolism in the protective response of LSCs to combined venetoclax and TKI therapy may extend to other BCR-ABL-driven malignancies. For instance, it would be critical to understand whether LIPA-dependent fatty acid generation is also involved in Philadelphia-positive B-cell acute lymphoblastic leukemia (B-ALL), where venetoclax and TKI dual therapy has shown early preclinical synergy.[9] If involved, blockade of free fatty acid production through LIPA inhibition would constitute a promising therapeutic strategy in combination with venetoclax/TKIs in this B-ALL subtype, associated with dismal survival rates in children and adults. Similarly, targeting fatty acid production may be beneficial in lymphoid blast phase CML cases, where current TKI and BCL-2 inhibitor combinations have been less successful.[10]

In summary, Minhajuddin et al.'s work advances our understanding of the preclinical efficacy of venetoclax and TKI combination therapy in bpCML with and without tyrosine kinase mutations, shedding light on the role of lysosomal function and fatty acid metabolism in treatment response. This research paves the way for exploring triple combinatorial therapies to enhance disease-free survival in bpCML patients, potentially transforming treatment approaches for this challenging condition in the future.

References

1. Minhajuddin M, Winters A, Ye H, et al. Lysosomal acid lipase A modulates leukemia stem cell response to venetoclax/tyrosine kinase inhibitor combination therapy in blast phase chronic myeloid leukemia. Haematologica. XXX
2. Hochhaus A, Baccarani M, Silver RT, et al. European LeukemiaNet 2020 recommendations for treating chronic myeloid leukemia. Leukemia. 2020;34(4):966-984.
3. Copland M, Hamilton A, Elrick LJ, et al. Dasatinib (BMS-354825) targets an earlier progenitor population than imatinib in primary CML but does not eliminate the quiescent fraction. Blood. 2006;107(11):4532-4539.
4. Carter BZ, Mak PY, Mu H, et al. Combined targeting of BCL-2 and BCR-ABL tyrosine kinase eradicates chronic myeloid leukemia stem cells. Sci Transl Med. 2016;8(355):355ra117.
5. Roberts AW, Wei AH, Huang DCS. BCL2 and MCL1 inhibitors for hematologic malignancies. Blood. 2021;138(13):1120-1136.
6. Goff DJ, Recart AC, Sadarangani A, et al. A Pan-BCL2 inhibitor renders bone-marrow-resident human leukemia stem cells sensitive to tyrosine kinase inhibition. Cell Stem Cell. 2013;12(3):316-328.
7. Adnan-Awad S, Kankainen M, Mustjoki S. Mutational landscape of chronic myeloid leukemia: more than a single oncogene leukemia. Leuk Lymphoma. 2021;62(9):2064-2078.
8. Hughes TP, Mauro MJ, Cortes JE, et al. Asciminib in Chronic Myeloid Leukemia after ABL Kinase Inhibitor Failure. N Engl J Med. 2019;381(24):2315-2326.
9. Moujalled DM, Hanna DT, Hediyeh-Zadeh S, et al. Cotargeting BCL-2 and MCL-1 in high-risk B-ALL. Blood Adv. 2020;4(12):2762-2767.
10. Parry N, Busch C, Aßmann V, et al. BH3 mimetics in combination with nilotinib or ponatinib represent a promising therapeutic strategy in blast phase chronic myeloid leukemia. Cell Death Discov. 2022;8(1):457.

Figure legends

Figure 1. Lysosomal acid lipase A (LIPA) modulates the response of blast phase chronic myeloid leukemia (bpCML) stem cells to venetoclax and tyrosine kinase inhibition. In bpCML, the combination of venetoclax and tyrosine kinase inhibitors (TKIs) upregulates LIPA and other lysosomal biology regulators, leading to increased free fatty acid production. Inhibiting LIPA or blocking free fatty acid upregulation sensitizes bpCML cells to venetoclax/TKI dual therapy.

- BCR-ABL
- BCR-ABL with T315I mutation
- BCR-ABL with other mutations