THERAPEUTIC ADVANCES in
Hematology

Letter to the Editor

Mechanisms of resistance to histone deacetylase inhibitors in acute leukemia

Ther Adv Hematol

2024, Vol. 15: 1–4

DOI: 10.1177/20406207241306553

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Keywords: acute leukemia, hematological malignancy, histone deacetylase inhibitors, treatment resistance

To the editor,

Histone deacetylase inhibitors (HDACis) have been explored since the early 2000s with notable success in treating certain lymphomas, which led to FDA approval for cutaneous T-cell lymphoma in 2006.[1] The recent article by Xiao et al. has broadly reviewed the role of HDACis in acute leukemia (AL).[2] However, it appears that the most important barrier in the routine clinical implementation of these agents may have been overlooked and remained underexplored. Despite preclinical success in leukemic models, the efficacy of HDACis in clinical settings remains limited, primarily due to resistance development. The latest studies have suggested combination therapies pairing HDACis with agents targeting complementary pathways—such as apoptotic regulators or DNA methyltransferase (DNMT) inhibitors—to enhance sensitivity and counteract resistance in AL.[3] Here, we address the molecular and cellular mechanisms and pathways contributing to HDACi resistance in AL.

Epigenetic compensation and redundant pathways

HDACis primarily target histone acetylation to promote chromatin relaxation and gene transcription. AL cells, however, can activate redundant pathways to maintain their malignant state. Compensatory upregulation of alternative epigenetic modifications, such as DNA methylation and histone methylation, can counteract the effects of HDACis by re-silencing tumor suppressor genes. For instance, increased DNMT activity can restore gene silencing in leukemic cells, evading HDACi-induced acetylation. Preclinical and early clinical studies have highlighted the efficacy of combining HDACis with DNMTis, such as azacitidine or decitabine, suggesting that dual inhibition may prevent re-silencing of critical tumor suppressor genes through a sustained epigenetic reprogramming that AL cells cannot easily bypass, potentially improving patient outcomes.[4]

Overexpression of efflux pumps

A chief barrier in treating AL with HDACi is drug efflux mediated by adenosine triphosphate-binding cassette (ABC) transporters. These transmembrane proteins actively contribute to reducing intracellular HDACi concentrations, thus limiting their efficacy. Overexpression of ABC transporters such as ABCB1 (P-glycoprotein) and ABCC1 (multidrug resistance-associated protein 1) has been implicated in HDACi resistance.[5] Clinical trials combining HDACis with ABC transporter inhibitors or alternative drug delivery methods, such as nanoparticle formulations, are currently under investigation.

Compensatory signaling pathways

In response to HDACi-induced cellular stress, AL cells activate compensatory signaling pathways that promote survival and reduce sensitivity to apoptosis. Notably, the PI3K/AKT/mTOR and MAPK pathways are upregulated in HDACi-resistant cells, promoting cell survival and proliferation despite HDACi treatment.[6] Preclinical evidence is in favor of increasing HDACi efficacy through the inhibition of these pathways.

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Altered expression of pro- and antiapoptotic genes

Resistance to HDACis often arises when AL cells adapt by upregulating the expression of antiapoptotic BCL-2, BCL-XL, or MCL-1. Downregulation of key pro-apoptotic genes like BAX and BAK reduces the leukemic cells' responsiveness to HDACis. Small-molecule inhibitors of anti-apoptotic proteins, such as the BCL-2 inhibitor venetoclax, are being explored as potential combinatory agents with HDACis.[7]

Epigenetic plasticity and cancer stem cells

Cancer stem cells (CSCs) exhibit significant epigenetic plasticity, enabling them to dynamically adapt to therapeutic pressure. CSCs in AL can survive HDACi treatment through reversible changes in gene expression that allow them to re-establish the leukemic cell population after drug withdrawal. This plasticity, combined with an ability to undergo quiescence, enables CSCs to evade HDACi-induced cell death and subsequently re-initiate leukemia. Although still under investigation, CSC-targeting agents, such as those involving Notch or Wnt signaling, may help eliminate CSCs when used in conjunction with HDACis.[8] Additionally, maintenance therapy with HDACis or other epigenetic modulators may prevent CSC-driven relapse in AL.

Table 1 summarizes the latest studies documenting clinical resistance to HDACis in AL patients. Future studies should focus on developing new generations of HDACis with improved selectivity and exploring combination regimens with potential efficacy enhancers, such as DNMTis and efflux pump inhibitors. Overcoming HDACi resistance holds the potential to transform the therapeutic landscape for patients with AL in the near future.

Table 1. Summary of early trials documenting clinical resistance to histone deacetylase inhibitors in acute leukemia.

Authors	Year	Patients	Treatment regimen	Findings
Wieduwilt et al.[9]	2019	Older patients with AML	Panobinostat (with daunorubicin and cytarabine)	Fifteen patients (60%) showed resistance to the treatment
Sayar et al.[10]	2019	Patients with relapsed/refractory AML	Vorinostat and sorafenib	Eight patients (50%) demonstrated resistance to the treatment
Goldberg et al.[11]	2020	Children with relapsed/refractory acute leukemia	Panobinostat	No response to treatment was observed in any of the patients
Wang et al.[12]	2020	Patients with relapsed/refractory AML	Chidamide and DCAG chemotherapy	Forty-two patients (45.2%) showed resistance to treatment
Holkova et al.[13]	2021	Patients with relapsed/refractory acute leukemia or MDS	Belinostat and bortezomib	Resistance to treatment was observed in 14 of 28 acute leukemia patients (50%)
Carraway et al.[14]	2021	ALL/ABL patients	Entinostat and clofarabine	Resistance to treatment and lack of response was seen in 18 of 28 patients (64.3%)
Shafer et al.[15]	2023	Relapsed/refractory AML and MDS patients	Belinostat and adavosertib	No responses were seen, with only nine patients with stable disease (55% resistance)
Garcia-Manero et al.[16]	2024	Adults with newly diagnosed AML	Pracinostat and azacitidine	From 203 patients receiving pracinostat, 125 (61.6%) showed clinical resistance to the treatment

ABL, acute biphenotypic leukemia; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; DCAG, decitabine, cytarabine, aclarubicin, and granulocyte colony-stimulating factor; MDS, myelodysplastic syndrome.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Author contributions
Mohammad Amin Akbarzadeh: Conceptualization; Investigation; Writing – review & editing.

Yosra Vaez-Gharamaleki: Investigation; Writing – original draft.

Mohammad-Salar Hosseini: Conceptualization; Investigation; Supervision; Writing – original draft.

Acknowledgement
None.

Funding
The authors received no financial support for the research, authorship, and/or publication of this article.

Competing interests
The authors declare that there is no conflict of interest.

Availability of data and materials
Not applicable.

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