Journal of Experimental and Clinical Medicine
https://dergipark.org.tr/omujecm

Research Article

J Exp Clin Med
2024; 41(3): 524-529
doi: 10.52142/omujecm.41.3.14

Targeting HDAC enzymes by SAHA enhances the cytotoxic effects of cisplatin on acute myeloid leukemia cells

Merve ŞANSAÇAR [1], Özge PEKİN [2], Emel Başak GENCER AKÇOK [2,*]

[1]Department of Bioengineering, Graduate School of Engineering and Science, Abdullah Gul University, Kayseri, Türkiye
[2]Department of Molecular Biology and Genetics, Faculty of Life and Natural Sciences, Abdullah Gul University, Kayseri, Türkiye

Received: 29.03.2024 • **Accepted/Published Online:** 25.04.2024 • **Final Version:** 30.09.2024

Abstract

Chemotherapy is a widely used therapeutic approach to combat hematopoietic malignancies such as acute myeloid leukemia (AML). Although cisplatin is known as the first-generation platinum-based chemotherapy inhibitor, the wide use of cisplatin eventually leads to drug resistance, which is the biggest impediment to cancer chemotherapy. Histone deacetylase enzyme (HDAC) inhibitors have the ability to induce cell cycle arrest and apoptosis in different types of cancer, which stands as a promising alternative for those cancer patients not appropriate for intensive chemotherapy. This study concluded that there was a significant decrease in the proliferation of MOLM-13 and MV4-11 FLT3-ITD+ AML cell lines with the increasing SAHA and cisplatin concentrations in 48 hours using MTT cell proliferation assay. Moreover, the combination of SAHA and cisplatin led to a reduction in the proliferation of both cell lines correlated with the synergistic effect of the two drugs depending on the combination index (CI). Furthermore, investigating apoptosis for combined administration resulted in increased induction of apoptosis by Annexin-V/PI double staining. In conclusion, although additional studies are needed to fully elucidate the molecular mechanism underlying this combination, we propose a new approach to targeting AML, as AML increases over time with drug resistance and the consequent year-on-year increase in patient mortality.

Keywords: histone deacetylase inhibitors, cisplatin, acute myeloid leukemia, combination treatment, apoptosis

1. Introduction

Acute myeloid leukemia (AML) is a hematopoietic malignant disorder that results from chromosomal rearrangements and multiple gene mutations in hematopoietic cells. These alterations prevent the production of differentiated and matured hematopoietic cells, promote the accumulation of leukemia blasts in the bone marrow and spread the peripheral blood (1, 2). The incidence of AML disease has been rising for the last 40 years, and this is correlated with the aging process (3). AML can have an impact on individuals of all ages; however, it predominantly affects adults (4). AML disease generally has been classified as a genetic disease; however, several recent studies report that epigenetic changes contribute to the progression of AML. The most common epigenetic regulation that regulates the chromatin structure and gene expressions are DNA methylation and histone modifications. These modifications are managed by the epigenetic regulatory enzymes, which are DNA methyltransferases (DNMTs), histone methyltransferases (HMTs), histone acetyltransferases (HATs), and histone deacetylases (HDACs). The dysfunctionality of these enzymes is observed in AML (5, 6). In this way, targeting epigenetic modifications could be an effective strategy in AML. The effect of hypomethylating agents in AML was approved, so the use of HDAC inhibitors (HDACis) is under clinical investigation and could be promising in AML treatments (7–9). HDACis promise a therapeutic strategy for AML therapy. The HDAC functions in many aspects of biological effects in cancer cells, such as induction of apoptosis, mitotic arrest, and activation of autophagy (10).

The regular cells are relatively resistant and irresponsive to cell death induced by HDACis, and this is the reason for using HDACi in cancer treatments (11, 12). Although HDAC enzyme inhibition could be used as the treatment approach, the HDACis are not effective as monotherapies. In contrast, a combination treatment strategy can be used with numerous anticancer drugs that demonstrate anti-leukemic activity. Furthermore, HDACis could induce differentiation, cell cycle arrest, and apoptosis in AML, which gives a good option for AML patients who are not appropriate for intensive chemotherapy. Many studies mentioned that after treatment with cisplatin, chemoresistance can be developed in many cancer types (13). In the present study, we aim to treat AML cell lines MOLM-13 and MV4-11, both possessing a common mutation on AML, which is the Fms Related Receptor Tyrosine Kinase 3 (FLT3), which harbors Internal Tandem Duplication (ITD), with the commonly used chemotherapeutic

*Correspondence: emelbasak.gencerakcok@agu.edu.tr

agent cisplatin in combination with SAHA. The combination therapy of cisplatin with HDACi is a promising strategy to enhance the efficacy of cisplatin (14). In this way, the success of treatment could be increased, and chemoresistance could be prevented by combining cisplatin with SAHA. Hence, we checked the anticancer effects of drugs using an MTT cell viability assay and investigated the anticancer effect using an apoptosis analysis. In conclusion, we suggested a combination treatment to overcome the proliferation of AML cells with the administration of SAHA and cisplatin by revealing the synergistical effect of both drugs.

2. Materials and Methods

2.1. Materials

Cisplatin and SAHA were purchased from Sigma. A 5 mM stock solution of SAHA was prepared in dimethylsulfoxide (DMSO), and 3.3 mM stock cisplatin solution was dissolved in NaCl in alignment with the proposed recommendations by the supplier, and the stock solutions were stored at -20ºC. The RPMI 1640 and penicillin/streptomycin were purchased from Euro Clone.

2.2. Cell Culture and Maintenance

The AML cell lines, MOLM- 13 and MV4-11, used in this study were obtained from the German National Resource Center for Biological Material (DSMZ). The cells were cultured in RPMI 1640 medium, which was supplemented with 10% FBS and 100 U/mL penicillin/streptomycin. The cells were kept at 37°C in an environment of 5% CO_2. Upon reaching confluency, the cells were seeded at a density of 1 x 10^6 cells/ml and subsequently split at ratios ranging from 1:2 every two days. Afterward, the cells were collected and subjected to centrifugation for 5 minutes at 700 rpm. The supernatant was discarded, and the pellet was reconstituted using fresh media.

2.3. Cell Viability Assay

The MTT (3-(4,5- dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide) assay was used to assess cell viability. Briefly, the cells were seeded in 96-well plates in triplicates, with a density of $1x10^4$ cells per well. Then, the cells were treated with varying concentrations of inhibitors alone and in combination for 48 hours. After the incubation, 10 µl of MTT solution was added to each well to initiate the assay, and then the plates were incubated at 37°C for 2-4 hours. Later, the 96-well plates were centrifuged at 1800 rpm for 10 minutes, and the supernatant was removed. Next, 100 µl of DMSO solution was added to each well to dissolve the formed formazan crystals, and the plates were incubated for an additional 15 minutes on a waving rotator in the dark at room temperature. Subsequently, the absorbance was measured at 570 nm using a Varioskan LUX multimode microplate reader from Thermo Scientific. The concentrations of SAHA and cisplatin that led to 20%, 30%, and 50% inhibition (known as IC20, IC30, and IC50) of MOLM-13 and MV4-11 cell lines were determined by analyzing the curves correlating cell proliferation with drug concentration. The combination analysis previously described was performed by using the CompuSyn software (Biosoft, Cambridge, United Kingdom) (15).

2.4. Cell Death Assay

The apoptotic cell death was assessed for cells treated with the IC50 value of SAHA and IC20 value of cisplatin in single and combinations using DMSO and NaCl as negative controls. The apoptotic cell population was determined by flow cytometry with Annexin V/Propidium iodide dual staining method as previously described (15). For this purpose, $1x10^6$ cells/well were incubated with inhibitors alone and their combinations. After 48 hours of incubation with drugs, the cells were harvested and analyzed using BD LSRFortessa (Becton Dickinson) flow cytometry.

2.5. Statistical Analysis

The GraphPad Prism 8 was used to analyze the data, and the comparisons of two experiment sets were performed by Two-Way ANOVA followed by Dunnett's Multiple Comparison test. The level of statistical significance was set at $P<0.05$.

3. Results

3.1. SAHA and Cisplatin Led to Decreased Cell Viability in AML Cells

To establish the efficacy of SAHA or cisplatin on the cell viability of MOLM-13 and MV4-11 AML cells, the cells were treated with increasing concentrations of SAHA and cisplatin alone. The results demonstrated that cell proliferation was reduced in a dose-dependent manner for both SAHA and cisplatin. When cisplatin was administered between 0.05-10 µM, the IC20, IC30 and IC50 values were determined as 0.53 µM, 1.03 µM and 2.62 µM for the MOLM-13 cells, respectively (Fig. 1A). For MV4-11, the same range of cisplatin dose was administered, and the IC20, IC30 and IC50 values were calculated as 0.156 µM, 0.79 µM and 3.38 µM, respectively (Fig. 1B). Afterward, MOLM-13 (0.05-2 µM) and MV4-11 (0.005-1 µM) cells were treated with SAHA. The IC20, IC30 and IC50 values of SAHA were specified as 0.073 µM, 0.09 µM and, 0.43 µM respectively for MOLM-13 cells and 0.0019 µM, 0.066 µM and 0.29 µM for MV4-11 cells, respectively (Fig. 1C and 1D). These results indicated that SAHA and cisplatin alone have an inhibitory effect on MOLM-13 and MV4-11 cell proliferation.

3.2. The Combinatorial Anticancer Effect of SAHA and Cisplatin on MOLM-13 and MV4-11 AML Cells

Next, to understand and investigate the effect of SAHA and cisplatin combination on MOLM-13 and MV4-11 cells, we treated cells with both drugs alone and combined IC20 and IC30 values. The SAHA or cisplatin administrations alone did not decrease the cell viability by less than 70%, as expected. However, when the combination of IC20 SAHA+IC20 cisplatin and IC30 SAHA+IC30 cisplatin was administered to the cells, MOLM-13 cells were more sensitive than MV4-11 cells. The cell viability was decreased by 56% and 68% for MOLM-13 cells in response to IC20 SAHA+IC20 cisplatin and IC30 SAHA+IC30 cisplatin combination, respectively (Fig. 2A). We also used the IC30 values of the drugs, and this

combination treatment resulted in a reduction of less than 50% in MOLM-13 AML cells. On the other hand, IC20 SAHA+IC20 cisplatin significantly reduced the cell viability of MV4-11 cells compared to single administrations and untreated control cells at 48 hours (Fig. 2B). In the administration of IC30 values of the inhibitors, the proliferation of MV4-11 cells was reduced by approximately 65%; however, no significant difference was observed compared to the IC30 cisplatin administration. Moreover, to determine whether the effect of these combinations was synergistic or not, the isobologram test was performed. The results indicated that the SAHA and Cisplatin combination treatments showed a CI value below 1.0 and, thus, a synergistic effect for both MOLM-13 and MV4-11 AML cells (Table 1).

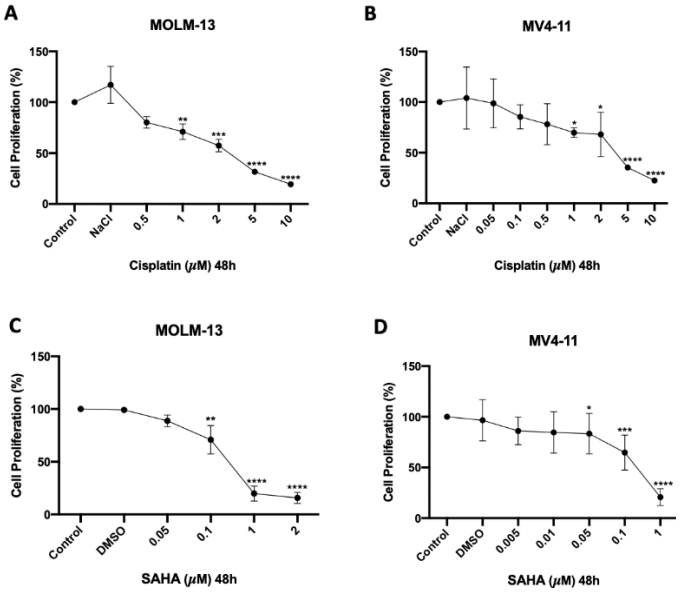

Fig. 1. The cytotoxic effect of Cisplatin (A, B) and SAHA (C, D) on MOLM-13 (A, C) and MV4-11 (B, D) AML cells. These results are representative of data from samples in triplicate in three independent experiments (n = 3). All data are presented as mean ± S.D. (ns=P > 0.05, *= P≤ 0.05, **= P ≤ 0.01, ***= P ≤ 0.001, ****= P≤ 0.0001)

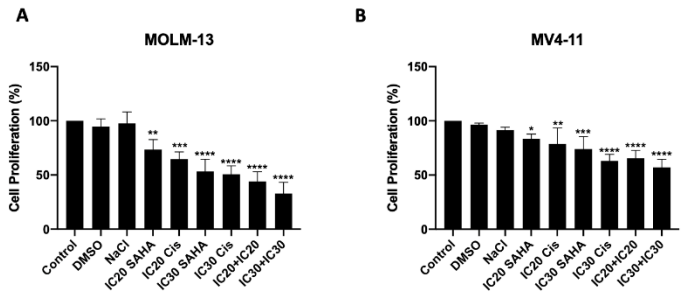

Fig. 2. The investigation of SAHA and Cisplatin combination on MOLM-13 (A) and MV4-11 (B) AML cell line. These results are representative of data from samples in triplicate in three independent experiments (n = 3). All data are presented as mean ± S.D. (ns=P > 0.05, *= P≤ 0.05, **= P ≤ 0.01, ***= P ≤ 0.001, ****= P≤ 0.0001)

Table 1. The combination index values of MOLM-13 and MV4-11 cells treated with the combination of SAHA with Cisplatin, were calculated and isobolograms were determined by CompuSyn software

MOLM-13			MV4-11		
SAHA (μM)	Cisplatin (μM)	SAHA + Cisplatin	SAHA (μM)	Cisplatin (μM)	SAHA + Cisplatin
Dose	Dose	CI Value	Dose	Dose	CI Value
0.073	0.53	0.39378	0.0019	0.156	0.24601
1.53	1.03	0.48659	0.066	0.79	0.59307

A CI of <1, =1, or >1 is indicative of synergistic, additive, or antagonistic effects, respectively

3.3. The Combination of SAHA and Cisplatin Induced Apoptotic Cell Death on AML Cells

We combined the IC50 value and 1 μM SAHA with the IC20 value of cisplatin, respectively, to investigate the mechanism behind the decreased cell viability. The administration of the IC50 value of SAHA and IC20 value of cisplatin in combination with MOLM-13 cells resulted in a 2.5-fold increase in total apoptotic cell death when compared to untreated control cells (Figure 3A). In particular, 1 μM SAHA and IC20 value of cisplatin led to a significant increase as such 7-fold for MOLM-13 cells. The single 1 μM SAHA administration and the combination with cisplatin caused a significant increase in total apoptotic cell death on MOLM-13 cells. Our results showed that the same combination experiment caused a 10-fold increase in late apoptotic cells compared to the control, while a single IC20 cisplatin treatment increased the amount of early apoptotic cells of MOLM-13 cells by 2.5-fold (Figure 3A). This result showed that the combination of 1 μM SAHA and cisplatin led to a better induction of apoptosis on MOLM-13 cells, considering the late and total apoptotic cell number. Similarly, MV4-11 cells were induced to undergo apoptosis in response to the same combination. The IC50 value of SAHA and IC20 of cisplatin combination resulted in a 2-fold increased apoptotic cell death in MV4-11 cells over 48 h compared to untreated controls (Figure 3B). Moreover, we demonstrated that administration of 1 μM SAHA and IC20 value of cisplatin led to an 8-fold more total apoptotic cell death, which was mostly composed of late apoptotic cells when compared to untreated MV4-11 control cells. Interestingly, unlike MOLM-13 cells, 1 μM SAHA treatment resulted in similar apoptotic cell death as in the IC50 SAHA+cisplatin combination. This result made us think that the apoptotic cell death in response to combination is mainly the effect of SAHA. In conclusion, our results demonstrated that the combination of SAHA and cisplatin increased the apoptotic cells for both cell lines but to a better extent for MOLM-13 cells.

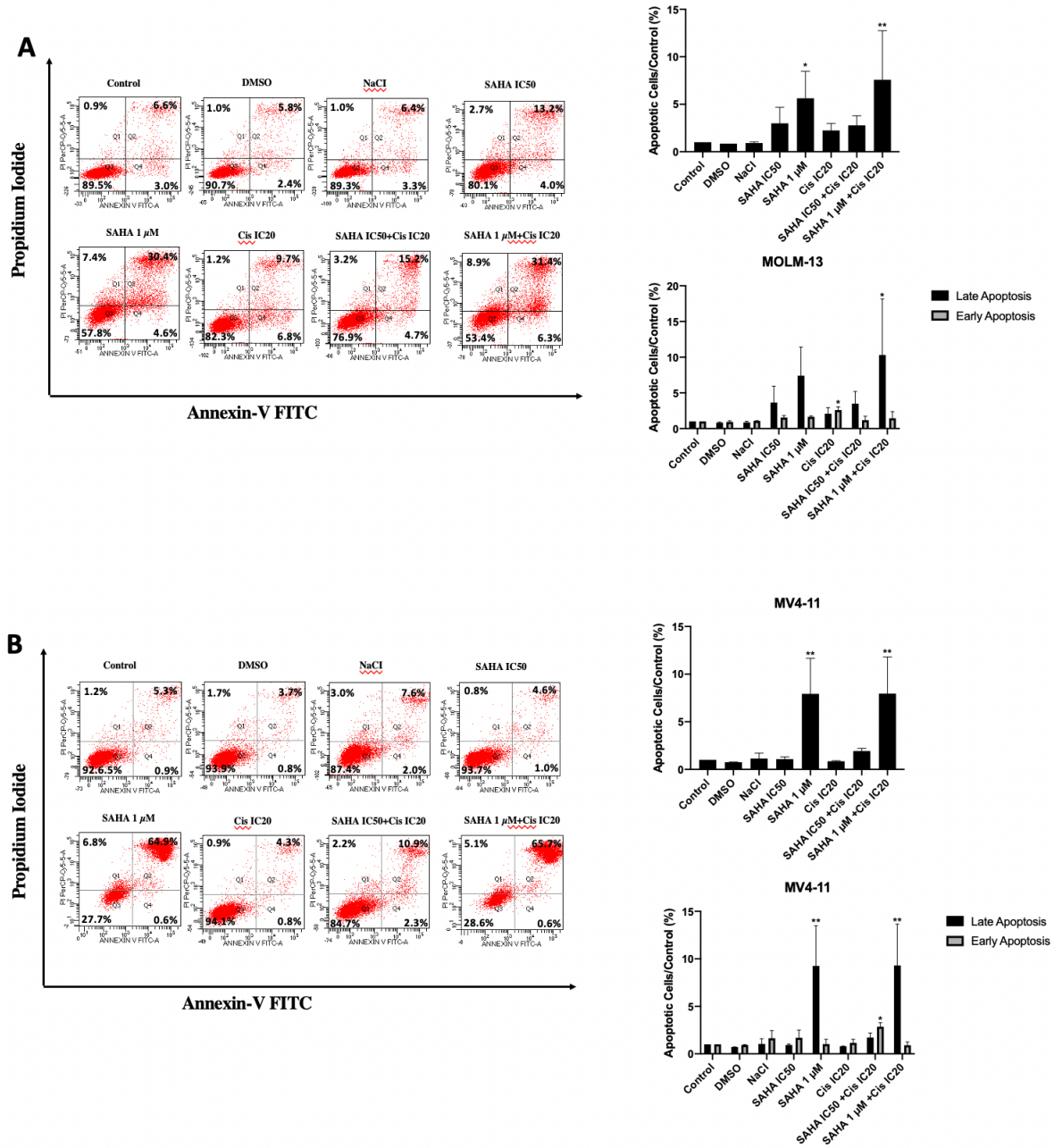

Fig 3. The apoptotic effect of SAHA and Cisplatin drug combination on MOLM-13 (A) and MV4-11 (B) AML cells. The experiments were performed as two biological replicates (n=2). The left part of the image indicates the representative apoptotic cell histograms. The graph where the right upper demonstrates the total apoptosis (Q2+Q4), the and below parts demonstrate the late (Q2) and early apoptotic (Q4) cell amount separately. All data are presented as mean ± S.D. (ns=P > 0.05, *= P≤ 0.05, **= P ≤ 0.01, ***= P ≤ 0.001, ****= P≤ 0.0001)

4. Discussion

Chemotherapy is a commonly used treatment method to combat various types of cancer. Despite the idea that chemotherapy fatally damages the DNA of cancer cells, its mutational effects in normal tissues have not yet been fully elucidated. One of these widely used chemotherapeutic agents recognized as the first-generation platinum-based chemotherapy inhibitor is cisplatin (16). Although cisplatin was first discovered as an agent that inhibits the growth of *Escherichia coli* after its cytotoxic effects on cancer cells have been proven, it has been used as a first-line therapeutic agent in clinics with numerous cancer types, especially leukemia. (17). When cisplatin enters the cell, it loses a chloride ligand, then binds to DNA, following the formation of intra-helix DNA adducts, and then inhibits DNA synthesis and, thus, growth of the cells. The cisplatin-induced DNA damage activates the DNA repair response via the nuclear excision repair system, stopping the cell death induced by cisplatin through the activation of the ATM pathway (18). Even though therapy has been indicated to be effective, many patients face relapses because of drug resistance. In this situation, researchers investigated the effect of combining cisplatin with different small inhibitors and natural products (19, 20).

Although there are effective and selective FLT3 tyrosine kinase inhibitors approved by the FDA and used in clinics, they might be ineffective in eliminating the FLT3-ITD+ AML cells, which in turn potentially cause relapse. It was shown that inhibition of FLT3 by tyrosine kinase inhibitors led to an upregulation of HDAC8 and activated the FLT3-ITD cells

(21). This study shows the link between the HDAC enzymes and the benefit of their inhibition against FLT3-ITD+ cells. In the present study, we aim to take a step towards developing novel approaches to eliminate FLT3-ITD+ AML cells. For this purpose, we treated two AML cells, MOLM-13 and MV4-11, both possessing a common mutation on AML, namely FLT3, which harbors ITD mutation (22). Specifically, these two AML cells were chosen to help compare our combination therapy because they possess the same mutation. As a first step, we administered the MOLM-13 and MV4-11 cells with both cisplatin and SAHA alone in different dose ranges individually. Administration of 10 μM cisplatin resulted in a reduction in proliferation of less than 90% for both cells. On the other hand, 1 μM SAHA resulted in 90% of death cells for MOLM-13 and MV4-11 cell lines. Consistent with our data, the data revealed by Ma et al. indicated that administration of SAHA (0.01–10 μM) for 72 hours resulted in a dose-dependent reduction of cell proliferation of MOLM-13 cells (23). Furthermore, the study by Yao et al. revealed that when 10 μM of SAHA was applied, approximately 80% reduction in proliferation was observed for MOLM-13 and MV4-11 cells (24). Similar to our data, Zhang et al. showed that cisplatin has a dose- and time-dependent increasing anticancer efficacy in human AML cell lines MV4-11 and MOLM-13 (25). Altogether, our data revealed the inhibitory effect of both SAHA and cisplatin in terms of cell proliferation for two AML cells.

As a further study, we continued with the combination of SAHA and cisplatin and evaluated this combination on the proliferation of MOLM-13 and MV4-11 FLT3-ITD+ AML cells. The results clearly show that the combined use of these two drugs has a synergistic anti-proliferative effect on these two AML cells compared to control and single administrations of SAHA and cisplatin. Similar to our results, the combination of SAHA and cisplatin significantly reduced VAT-39 cell viability of hepatoid adenocarcinoma cells in a dose-dependent manner (26). In addition, Jin et al. reported the cytotoxic effect of SAHA and cisplatin combination therapy on HeLa cells (27). Moreover, the data revealed by Shen and his colleagues indicated that a combination of SAHA and cisplatin results in a marked increase in cytotoxicity of human oral squamous cell carcinoma and osteosarcoma cells (28, 29). Furthermore, the results have shown that SAHA significantly reduced cell viability and synergistically enhanced the anticancer effects of cisplatin in both the cisplatin-resistant head and neck cancer cells (30).

To further investigate, we evaluated the effect of the mentioned combinations in terms of programmed cell death; apoptosis. With this aim, the cells were treated with both alone and in combinations of IC50 value of SAHA, 1 μM of SAHA and IC20 value of cisplatin and analyzed by flow cytometer. Interestingly, following the IC50 values of SAHA and cisplatin, IC20 was not statistically significant; increasing the SAHA to 1 μM with IC20 of cisplatin resulted in induce total apoptotic cell death for both AML cells. Compatible with our data, while administration of SAHA (2.5 μM) or cisplatin (10 μM) alone induced moderate apoptosis on HeLa cells, co-administration of cisplatin (10 μM) and SAHA (2.5 μM) resulted in a significantly higher degree of induction of apoptosis when it compared to cisplatin alone (27). The co-treatment of SAHA and cisplatin led to an induced apoptosis in human oral squamous cell carcinoma cell lines after being evaluated by TUNEL assay (28). The study by Kyaw et al. showed that the number of apoptotic cells was 2.2 times higher in cells treated with cisplatin and 3.3 times higher in cells treated in combination with cisplatin and SAHA compared to control cells (26). However, single 1 μM SAHA resulted similarly to the combination with IC20 cisplatin in MV4-11 cells. This aforementioned situation led us to the idea that SAHA administration alone may also cause apoptotic cell death. To fully explain this, further analysis could be used to check for different apoptotic mechanisms, such as checking the expression level of anti-apoptotic or pro-apoptotic proteins to fully elucidate the apoptotic mechanism behind them. Although further studies about the mentioned combination effect on AML is needed, in conclusion, our study proposes simultaneous administration of SAHA and cisplatin to inhibit cell proliferation of MOLM-13 and MV4-11 cell lines in AML with induction of apoptotic cell death.

Conflict of interest

The authors declared no conflict of interest.

Funding

This study was not supported by any funding agencies.

Acknowledgments

The authors would like to thank the flow cytometry facility at Abdullah Gül University Central Research Laboratory. The authors wish to thank Esma Saraymen, the flow cytometry specialist, for her technical assistance during flow cytometry experiments.

Authors' contributions

Concept: E.B.G.A., Design: E.B.G.A., Data Collection or Processing: M.Ş., Ö.P., Analysis or Interpretation: M.Ş., Ö.P., Literature Search: M.Ş., Ö.P., Writing: E.B.G.A., M.Ş.

References

1. Rubnitz JE, Gibson B, Smith FO. Acute Myeloid Leukemia. Pediatr Clin North Am. 2008;55(1):21–51.
2. Prada-Arismendy J, Arroyave JC, Röthlisberger S. Molecular biomarkers in acute myeloid leukemia. Blood Rev. 2017;31(1):63–76.
3. Brown E, Guinn B ann. Molecular Mechanisms and Therapies of Myeloid Leukaemia. Int J Mol Sci. 2022;23(11):6251.
4. Carter JL, Hege K, Yang J, Kalpage HA, Su Y, Edwards H, et al. Targeting multiple signaling pathways: the new approach to acute myeloid leukemia therapy. Signal Transduct Target Ther. 2020 Dec 18;5(1):288.
5. Zhang J, Gao X, Yu L. Roles of Histone Deacetylases in Acute Myeloid Leukemia With Fusion Proteins. Front Oncol.

2021;11:741746.

6. Liu P, Yang F, Zhang L, Hu Y, Chen B, Wang J, et al. Emerging role of different DNA methyltransferases in the pathogenesis of cancer. Front Pharmacol. 2022;13:958146.
7. San José-Enériz, Gimenez-Camino, Agirre, Prosper. HDAC Inhibitors in Acute Myeloid Leukemia. Cancers (Basel). 2019;11(11):1794.
8. Quintás-Cardama A, Santos FPS, Garcia-Manero G. Histone deacetylase inhibitors for the treatment of myelodysplastic syndrome and acute myeloid leukemia. Leukemia. 2011;25(2):226–35.
9. San José-Enériz, Gimenez-Camino, Agirre, Prosper. HDAC Inhibitors in Acute Myeloid Leukemia. Cancers (Basel). 2019;11(11):1794.
10. Li Y, Seto E. HDACs and HDAC Inhibitors in Cancer Development and Therapy. Cold Spring Harb Perspect Med. 2016;6(10):a026831.
11. Ungerstedt JS, Sowa Y, Xu WS, Shao Y, Dokmanovic M, Perez G, et al. Role of thioredoxin in the response of normal and transformed cells to histone deacetylase inhibitors. Proc Natl Acad Sci U S A. 2005;102(3):673-8.
12. Konsoula Z, Velena A, Lee R, Dritschilo A, Jung M. Histone Deacetylase Inhibitor: Antineoplastic Agent and Radiation Modulator. Adv Exp Med Biol. 2011;720:171-9..
13. Siddik ZH. Cisplatin: mode of cytotoxic action and molecular basis of resistance. Oncogene. 2003;22(47):7265–79.
14. Suraweera A, O'Byrne KJ, Richard DJ. Combination Therapy With Histone Deacetylase Inhibitors (HDACi) for the Treatment of Cancer: Achieving the Full Therapeutic Potential of HDACi. Front Oncol. 2018;8:92.
15. Şansaçar M, Sağır H, Gencer Akçok EB. Inhibition of PI3K-AKT-mTOR pathway and modulation of histone deacetylase enzymes reduce the growth of acute myeloid leukemia cells. Med Oncol. 2023;41(1):31.
16. 1Ghosh S. Cisplatin: The first metal based anticancer drug. Bioorg Chem. 2019;88:102925.
17. Lugones Y, Loren P, Salazar LA. Cisplatin Resistance: Genetic and Epigenetic Factors Involved. Biomolecules. 2022;12(10):1365.
18. Galluzzi L, Senovilla L, Vitale I, Michels J, Martins I, Kepp O, et al. Molecular mechanisms of cisplatin resistance. Oncogene. 2012;31(15):1869–83.
19. Minerva, Bhat A, Verma S, Chander G, Jamwal RS, Sharma B, et al. Cisplatin-based combination therapy for cancer. J Cancer Res Ther. 2023;19(3):530–6.
20. Dasari S, Njiki S, Mbemi A, Yedjou CG, Tchounwou PB. Pharmacological Effects of Cisplatin Combination with Natural Products in Cancer Chemotherapy. Int J Mol Sci. 2022;23(3):1532.
21. Long J, Jia MY, Fang WY, Chen XJ, Mu LL, Wang ZY, et al. FLT3 inhibition upregulates HDAC8 via FOXO to inactivate p53 and promote maintenance of FLT3-ITD+ acute myeloid leukemia. Blood. 2020;135(17):1472–83.
22. Skopek R, Palusińska M, Kaczor-Keller K, Pingwara R, Papierniak-Wyglądała A, Schenk T, et al. Choosing the Right Cell Line for Acute Myeloid Leukemia (AML) Research. Int J Mol Sci. 2023;24(6):5377.
23. Ma X, Zhao M, Wu ZX, Yao J, Zhang L, Wang J, et al. The Histone Deacetylase Inhibitor I13 Induces Differentiation of M2, M3 and M5 Subtypes of Acute Myeloid Leukemia Cells and Leukemic Stem-Like Cells. Front Oncol. 2022;12:855570.
24. Yao J, Li G, Cui Z, Chen P, Wang J, Hu Z, et al. The Histone Deacetylase Inhibitor I1 Induces Differentiation of Acute Leukemia Cells With MLL Gene Rearrangements via Epigenetic Modification. Front Pharmacol. 2022;13:876076.
25. Zhang Y, Wang L, Zi Y, Zhang L, Guo Y, Huang Y. Oridonin effectively reverses the drug resistance of cisplatin involving induction of cell apoptosis and inhibition of MMP expression in human acute myeloid leukemia cells. Saudi J Biol Sci. 2017;24(3):678–86.
26. Kyaw MTH, Yamaguchi Y, Choijookhuu N, Yano K, Takagi H, Takahashi N, et al. The HDAC Inhibitor, SAHA, Combined with Cisplatin Synergistically Induces Apoptosis in Alpha-fetoprotein-producing Hepatoid Adenocarcinoma Cells. Acta Histochem Cytochem. 2019;52(1):1–8.
27. Jin KL, Park JY, Noh EJ, Hoe KL, Lee JH, Kim JH, et al. The effect of combined treatment with cisplatin and histone deacetylase inhibitors on HeLa cells. J Gynecol Oncol. 2010;21(4):262.
28. Shen J, Huang C, Jiang L, Gao F, Wang Z, Zhang Y, et al. Enhancement of cisplatin induced apoptosis by suberoylanilide hydroxamic acid in human oral squamous cell carcinoma cell lines. Biochem Pharmacol. 2007;73(12):1901–9.
29. Hou M, Huang Z, Chen S, Wang H, Feng T, Yan S, et al. Synergistic antitumor effect of suberoylanilide hydroxamic acid and cisplatin in osteosarcoma cells. Oncol Lett. 2018;16(4):4663-4670;
30. Kumar B, Yadav A, Lang JC, Teknos TN, Kumar P. Suberoylanilide hydroxamic acid (SAHA) reverses chemoresistance in head and neck cancer cells by targeting cancer stem cells via the downregulation of nanog. Genes Cancer. 2015;6(3–4):169–81.