

DISULFIRAM AND METFORMIN COADMINISTRATION EXHIBITS ANTICANCER EFFECT ON FIBROSARCOMA IN HAMSTERS

Dušica J. Popović¹, Kosta J. Popović², Dejan Miljković¹, Dušan Lalošević¹, Ivan Čapo¹ and Jovan K. Popović³

¹Department of Histology and Embryology, Faculty of Medicine, University of Novi Sad, Novi Sad, Republic of Serbia,

²Department of Pharmacy, Faculty of Medicine, University of Novi Sad, Novi Sad, Republic of Serbia,

³Department of Pharmacology, Toxicology and Clinical Pharmacology, Faculty of Medicine, University of Novi Sad, Novi Sad, Republic of Serbia

KEYWORDS: disulfiram; metformin; fibrosarcoma; hamsters; anticancer effects

INTRODUCTION

We investigated the effect of disulfiram and metformin on fibrosarcoma in hamsters. Aldehyde dehydrogenase (ALDH) is a cancer stem cell marker, associated with chemoresistance. Disulfiram, an alcohol aversion agent, is well known ALDH and proteasome inhibitor. Disulfiram inhibits growth of various cancer cell lines and is a candidate for repurposing in oncology.¹⁻³.

OBJECTIVES

Objective of the research was to prove that coadministration of disulfiram and metformin exhibits anticancer effects *in vivo* on fibrosarcoma inoculated to hamsters.

METHOD / DESIGN:

The 40 Syrian golden hamsters of approximately 90 g, both sexes, were randomly allocated in 3 experimental and 1 control groups of 10 animals in each. 2×10^6 BHK-21/C13 cells in 1ml were injected subcutaneously on the back of animals in 4 groups. The first experimental group started peroral treatment with metformin 500 mg/kg daily, second with disulfiram 200 mg/kg daily and third with combination of metformin 500 mg/kg and disulfiram 200 mg/kg daily, via gastric probe 3 days before tumor inoculation. After 19 days, when tumors were approximately 2-3 cm in control group, all animals were sacrificed, blood collected for glucose and other analyses, tumors excised, weighed, diameters measured, tumor samples pathohistologically (HE) and immunohistochemically (Ki-67, CD 31, COX IV, GLUT-1, iNOS) assessed (Figure) and main organs toxicologically analyzed, including control animals receiving metformin and disulfiram. Tumor volume was determined using the water displacement method and formula $L \times S^2 / 2$, L - the longest, S - the shortest diameter. Ki-67-positive cells in the tumor samples were quantified, images were taken and processed by software UTHSCSA Image Tools for Windows Version 3.00. Statistical significances were determined by the one way ANOVA.

RESULTS

The combination of disulfiram and metformin inhibited fibrosarcoma growth in hamsters without toxicity.

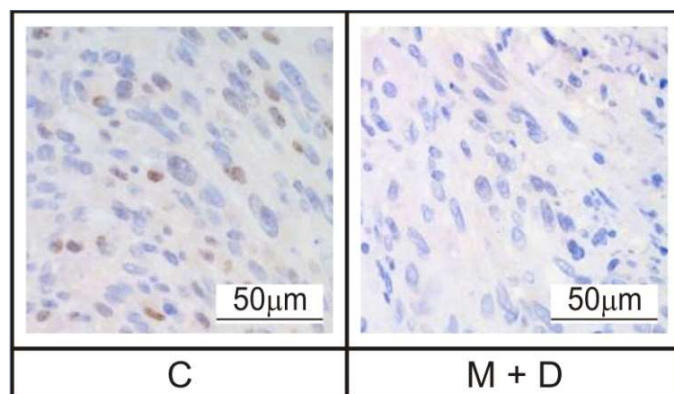


Figure. Illustration of experimental methodology. BHK fibrosarcoma immunohistochemical assessment of Ki-67 - proliferation marker protein: C – control group, M+D – group treated with combination of metformin and disulfiram.

CONCLUSIONS

Administration of disulfiram with metformin might be an effective and safe approach in novel nontoxic adjuvant anticancer treatment and relapse prevention antitumor therapy.

ACKNOWLEDGEMENTS

This study was supported by the Republic of Serbia, Autonomous Province of Vojvodina, Provincial Secretariat for High Education and Scientific Research [Project title: Discovery of effective non-toxic anticancer drug combinations on experimental fibrosarcomas, grant no. 142-451-2498/2021-03 (Project leader Dušica Popović)] and Republic of Serbia, Ministry of Science [grant no. 172013].

REFERENCES

- Popović DJ, Lalošević D, Miljković D, Popović KJ, Čapo I, Popović JK. Effect of metformin on fibrosarcoma in hamsters. *Eur. Rev. Med. Pharmacol. Sci.* 2017; 21(23): 5499-5505.
- Li, Y., Chen, F., Chen, J., Chan, S., He, Y., Liu, W., Zhang, G., 2020. Disulfiram/Copper Induces Antitumor Activity against Both Nasopharyngeal Cancer Cells and Cancer-Associated Fibroblasts through ROS/MAPK and Ferroptosis Pathways. *Cancers (Basel)*, 12(1), 138.
- Popović KJ, Popović DJ, Miljković D, Popović JK, Lalošević D, Čapo I. Co-treatment with nitroglycerin and metformin exhibits physicochemically and pathohistologically detectable anticancer effects on fibrosarcoma in hamsters. *Biomed. Pharmacother.* 2020; 130: 110510.

CONTACT

Corresponding author:

jovan.popovic@mf.uns.ac.rs;

jovapopmf@gmail.com