

THE USE OF METFORMIN AS ADJUVANT TO REVERSE ALLANTOIN-REDUCED CYTOTOXICITY OF CISPLATIN *IN VITRO*

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Introduction and objective: Tumor Lysis Syndrome (TLS) is a metabolic disorder that mainly affects malignant hematological neoplasms patients, and its development is frequently related to uric acid accumulation (hyperuricemia) due to high DNA degradation during chemotherapy. Rasburicase® is a recombinant urate oxidase enzyme applied to treat and avoid TLS, converting urate in allantoin, a compound easily eliminated by the kidneys. However, in a recent study, our group showed *in vitro*, that high allantoin concentration, as observed in oncological patients under rasburicase treatment, reduces cisplatin cytotoxicity in non-small cell lung cancer cell line (H460). Thus, understanding the importance of maintaining the concomitant use of cisplatin and rasburicase for oncological patients, mainly for CML patients due the higher incidence of TLS among these patients, look for adjuvant agents that can restores cisplatin cytotoxicity it is of great interest. Among these, metformin stands out for its effectiveness, safety, in addition to others pharmacological parameters already established. Metformin is a biguanide drug used as first line treatment for type 2 diabetes *mellitus* (T2DM) patients, due to its anti-hyperglycemic effect. Beyond the use of metformin to treat T2DM patients, many studies had already demonstrated the antitumoral effects of metformin either as monotherapy or as adjuvant with other drugs. We have evaluated metformin's capacity in restores allantoin-reduced cisplatin cytotoxicity in the chronic myeloid leukemia cell line (K562) *in vitro*. **Materials and methods:** The cells were maintained in RPMI 1640 medium supplemented with 10% FBS and 0.5% PS under 37°C and 5% CO₂. For the experiments the cells were treated

with metformin (0.1, 0.25, 0.5, 0.6025, 2, 2.5 and 3mM), cisplatin (15, 16.5, 20, 30 and 33 μ M), allantoin (100 and 200 μ g/ml) and their combinations under low glucose availability (0.5mM) for 48h. Cell viability, cell cycle, morphology analysis and NMR spectroscopy were performed. **Results and conclusion:** Our results showed that allantoin reduces cisplatin cytotoxicity in K562 cell line; metformin synergistically increased cisplatin's cell death; metformin was capable to restore cisplatin cytotoxicity before reduced by allantoin. We also observed the absence of interaction between metformin and cisplatin and a possible interaction between metformin and allantoin. Through the obtained results, we can conclude that metformin exerts its adjuvant effect in restores cisplatin efficacy reduced by allantoin.

Keywords: Metformin, Cisplatin, Allantoin.

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