Influence of DNA Damage Response Mechanisms in Leukemia Cells Resistant to the Antineoplastic Mitoxantrone

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**Introduction and Objectives:** Chemotherapy is one of the main cancer treatment strategies; however, tumors can show resistance, which makes the treatment partial or totally inefficient. Among the mechanisms that may be related to the resistant profile, the most studied is increased drug efflux through ABC transporter permeases. On the other hand, altered DNA repair pathways may contribute to cancer resistance, since the lesions are removed before they become toxic to cells, which reduces chemotherapy effectiveness. Among DNA repair pathways, Nucleotide Excision Repair (NER) is one of the most versatile, and there are studies showing its involvement in removal of anthracyclines-induced lesions. Thus, our aim was to evaluate the contribution of DNA damage response (DDR) mechanisms, focusing on NER, to the resistance to mitoxantrone (MXT), an anthracycline analog, using the mitoxantrone-resistant leukemia cell line HL-60/MX2 as a model.

**Materials and Methods:** After treatment with MXT and etoposide (ETO), a topoisomerase II inhibitor, cell survival was assessed by trypan blue exclusion method; cell cycle profile and H2AX histone phosphorylation (γH2AX) were evaluated by flow cytometry; and gene expression levels of NER and efflux proteins were determined by RT-qPCR.

**Results and Conclusions:** Results indicate a different response, mainly time-dependent, between the resistant HL-60/MX2 and the sensitive HL-60 cells, as observed in the survival assay, cell cycle, and H2AX phosphorylation profile. Furthermore, in the resistant cells, RT-qPCR analysis showed an increase in the expression of NER genes, with ERCC1 expression increased before and after treatments, and XPA mainly after the treatments. In conclusion our results show that ABC proteins do not mediate the resistance of HL-60/MX2, and indicate the contribution of NER machinery in the resistance of these cells to MXT and ETO.

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**Key words:** cancer, DNA repair, tumor resistance.