

**THE GENOTOXICITY OF AMSACRINE IN NORMAL CELLS AND
CANCER CELLS**JANUSZ BŁASIAK and EWA GLOC

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Amsacrine is an acridine derivative drug applied in haematological malignancies. It targets topoisomerase II, enhancing the formation of a cleavable DNA-enzyme complex and leading to DNA fragmentation in dividing cancer cells. Little is known about other modes of interaction of amsacrine with DNA, modes by which it could also affect normal cells. Using the alkaline comet assay, we showed that amsacrine at concentrations in the range 0.01-10 μM induced DNA damage in normal human lymphocytes and human promyelocytic leukemia HL-60 cells lacking the *p53* gene. The effect was dose-dependent. Treated cells were able to recover within a 120 minute incubation. Amifostine at 14 mM decreased the level of DNA damage in normal lymphocytes and had no effect on the HL-60 cells. Vitamin C at 10 and 50 μM diminished the extent of DNA damage in normal lymphocytes, but had no effect in cancer cells. Pretreatment of the cells with the nitron spin trap, *N-tert-butyl- α -phenylnitron*, or ebselen, which mimics glutathione peroxidase, reduced the extent of DNA damage evoked by amsacrine in normal and malignant cells. The cells exposed to amsacrine and treated with endonuclease III and 3-methyladenine-DNA glycosylase II, the enzymes recognizing oxidized and alkylated bases, respectively, displayed a greater extent of DNA damage than those not treated with these enzymes. The results obtained suggest that free radicals may be involved in the formation of DNA lesions induced by amsacrine. The drug can also methylate DNA bases. Our results indicate that the induction of secondary malignancies should be taken into account as diverse side effects of amsacrine. Amifostine and vitamin C can be considered as protective agents against DNA damage in normal cells.

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