Cisplatin resistance analysis: Insights on the usefulness of accurate DNA adducts quantitation

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Although cisplatin (cis-diamminedichloroplatinum (II) or cDDP) is one of the most extensively, and rather successfully, chemotherapy drugs used in the treatment of several types of tumors, it presents the important drawbacks of toxicity and especially patient resistance. This resistance, acquired or innate, might be the result of several different processes that are ultimately related either with preventing DNA adduct formation, or with their fast removal from the exposed cell DNA. Thus, the accurate detection and quantitation of adducts might be a valuable tool in the early prediction of cisplatin resistance. Using four human cell lines of different origins and cisplatin sensitivities (A549, GM04312, A2780 and A2780cis), and low cisplatin doses (5, 10 and 20 μM for 3 hours), the relevance of DNA adduct levels as potential predictor of viability and apoptosis (used as resistance indicators) was studied alone and in combination with the intracellular Pt content, the induced genomic instability (measured with the comet assay), and the induced cell cycle alterations. Uni- and multi-variate linear regression analyses were used in this study. Cell viability, apoptosis and cell cycle changes were estimated 24 h after the end of treatment. Intracellular Pt content, adducts levels and genomic instability were determined immediately after treatment and also one hour later. Results show that cisplatin-induced G-G intra-strand adducts were detected at all concentrations and that they were the best predictor for viability and apoptosis in all the studied cell lines. The prediction improved when comet results were included in the analysis, especially in the ovarian A2780 and A2780cis cell lines.