DNA mismatch repair defect and sensitivity of tumor cells to liposomal formulations of platinum drugs

Summary / Zusammenfassung
Lipoplatin, currently under Phase III evaluation, is a novel liposomal Cisplatin formulation highly effective against cancers. Lipoplatin has eliminated or reduced the systemic toxicity frequently seen for Cisplatin. The objective of the present study was to determine whether the cytotoxic effect of Lipoplatin is dependent on the functional integrity of DNA mismatch repair (MMR), a post-replicative DNA repair machinery implicated in cell cycle control and apoptosis. A 2-fold resistance to Lipoplatin of HCT116 human colorectal adenocarcinoma cells lacking MLH1, one of five proteins crucial to MMR function, as compared to MLH1-expressing HCT116 cells. In addition, MLH1-deficient cells were at least 3-fold less susceptible to apoptosis (DNA fragmentation) than MLH1-proficient cells. However, proteolytic processing of caspase-3, caspase-7, and PARP-1 following Lipoplatin treatment was comparable in MLH1-deficient cells and MLH1-proficient cells. Furthermore, MLH1-deficient cells retained the ability to attenuate cell cycle progression past the G2/M checkpoint following Lipoplatin treatment. In conclusion, our results indicate that the Lipoplatin sensitivity phenotype of MLH1-proficient cells correlated with increased apoptosis which may occur via caspase-independent pathways. They also suggest that the integrity of MMR function is a relevant determinant accounting for the cytotoxicity of Lipoplatin. This, however, does not seem to apply to Lipoxal, a novel liposomal formulation of Oxaliplatin, because MLH1-deficient cells were as sensitive to Lipoxal as MLH1-proficient cells.

Publications / Publikationen
André Fedier, Cédric Poyet, Daniele Perucchini, Teni Boulikas, and Daniel Fink. (2006) MLH1-deficient tumour cells are resistant to lipoplatin but retain sensitivity to lipoxal. Anti-Cancer Drugs 17: 315-323.

Keywords / Suchbegriffe
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