Low oxygen tension reverses antineoplastic effect of iron chelator deferasirox in human glioblastoma cells

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Résumé en anglais	Background Overcoming resistance to treatment is an essential issue in many cancers including glioblastoma (GBM), the deadliest primary tumor of the central nervous system. As dependence on iron is a key feature of tumor cells, using chelators to reduce iron represents an opportunity to improve conventional GBM therapies. The aim of the present study was, therefore, to investigate the cytostatic and cytotoxic impact of the new iron chelator deferasirox (DFX) on human GBM cells in well-defined clinical situations represented by radiation therapy and mild-hypoxia. Results Under experimental normoxic condition (21 % O2), deferasirox (DFX) used at 10 µM for 3 days reduced proliferation, led cell cycle arrest in S and G2-M phases and induced cytotoxicity and apoptosis in U251 and U87 GBM cells. The abolition of the antineoplastic DFX effects when cells were co-treated with ferric ammonium sulfate supports the hypothesis that its effects result from its ability to chelate iron. As radiotherapy is the main treatment for GBM, the combination of DFX and X-ray beam irradiation was also investigated. Irradiation at a dose of 16 Gy repressed proliferation, cytotoxicity and apoptosis, but only in U251 cells, while no synergy with DFX was observed in either cell line. Importantly, when the same experiment was conducted in mild-hypoxic conditions (3 % O2), the antiproliferative and cytotoxic effects of DFX were abolished, and its ability to deplete iron was also impaired. Conclusions Taken together, these in vitro results could raise the question of the benefit of using iron chelators in their native forms under the hypoxic conditions often encountered in solid tumors such as GBM. Developing new chemistry or a new drug delivery system that would keep DFX active in hypoxic cells may be the next step toward their application.
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