Abstract

The numerical and structural chromosomal instability seen in cancer cells is related to several cellular mechanisms of importance to the cellular response to irradiation and, consequently, to its therapeutic effect. In this work, multiple markers of chromosomal instability as well as the effect of the potential radiosensitizer pentoxifylline at different radiation doses and dose rates have been studied and correlated to the degree of radiosensitivity and cell cycle effects. The aim was to optimize the radiotherapy of individual tumours and to design strategies for improving the therapeutic ratio.

The radiosensitivity *in vitro* on established head and neck cell lines was measured using the clonogenic survival assay and different DNA analysis methods. This thesis demonstrates and discusses the complexities of potential predictive marker profiles in these cell lines and the insufficiency of using these markers separately as single markers to predict radiosensitivity *in vitro*. A positive correlation among the studied cell lines between the number of chromosomal arms involved in DNA copy number changes and increasing surviving fractions at 2 Gy was found.

Previous investigations on the potential radiosensitizing properties of pentoxifylline have focused on its effect on tumour tissue perfusion and its ability to decrease the influence of hypoxia *in vivo*. This study shows that cells derived from tumour tissue in the head and neck with various properties governing radiosensitivity can be sensitized by pentoxifylline *in vitro*. Furthermore, our sub-classification of studied cell lines based on their genomic profile is important when validating potential radiosensitizers targeting a specific gene or signalling pathway.

The observations on the radiosensitization potential of pentoxifylline *in vitro* made it interesting to analyse the combination of pentoxifylline with low-dose-rate irradiation, with the additional aim of shedding more light on the molecular mechanisms underlying the radiosensitizing effects of the drug. Moreover, redistribution of cells into the G_2 phase through low-dose-rate irradiation and release of cells blocked in the G_2 phase by pentoxifylline would both be dependent on proliferation rate and impaired molecular stress pathways. The enhancement in the cytotoxic effect of pentoxifylline was statistically significant after high-dose-rate irradiation as well as after low-dose-rate irradiation in the tested cell lines.

The observed radiosensitizing effect of pentoxifylline at low-dose-rate irradiation compared to high-dose-rate irradiation for cell lines with different proliferation rates indicates that pentoxifylline in combination with low-dose-rate irradiation is worth further study, both *in vitro*, for disclosing underlying mechanisms, and *in vivo*, to confirm the findings.