Alpha-particle emitting 213Bi-anti-EGFR immunoconjugates eradicate tumor cells independent of oxygenation.

Abstract:
Hypoxia is a central problem in tumor treatment because hypoxic cells are less sensitive to chemo- and radiotherapy than normoxic cells. Radioresistance of hypoxic tumor cells is due to reduced sensitivity towards low Linear Energy Transfer (LET) radiation. High LET ß-emitters are thought to eradicate tumor cells independent of cellular oxygenation. Therefore, the aim of this study was to demonstrate that cell-bound ß-particle emitting (213)Bi immunoconjugates kill hypoxic and normoxic CAL33 tumor cells with identical efficiency. For that purpose CAL33 cells were incubated with (213)Bi-anti-EGFR-MAb or irradiated with photons with a nominal energy of 6 MeV both under hypoxic and normoxic conditions. Oxygenation of cells was checked via the hypoxia-associated marker HIF-1α. Survival of cells was analysed using the clonogenic assay. Cell viability was monitored with the WST colorimetric assay. Results were evaluated statistically using a t-test and a Generalized Linear Mixed Model (GLMM). Survival and viability of CAL33 cells decreased both after incubation with increasing (213)Bi-anti-EGFR-MAb activity concentrations (9.25 kBq/ml-1.48 MBq/ml) and irradiation with increasing doses of photons (0.5-12 Gy). Following photon irradiation survival and viability of normoxic cells were significantly lower than those of
hypoxic cells at all doses analysed. In contrast, cell death induced by (213)Bi-anti-EGFR-MAb turned out to be independent of cellular oxygenation. These results demonstrate that ?-particle emitting (213)Bi-immunoconjugates eradicate hypoxic tumor cells as effective as normoxic cells. Therefore, (213)Bi-radioimmunotherapy seems to be an appropriate strategy for treatment of hypoxic tumors.

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