Boosting Oxygen Diffusion in the Radioresistant Oesophageal Tumour Microenvironment to Improve Radiotherapy.

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Purpose/ Objective

Oesophageal adenocarcinoma (OAC) is a poor prognosis cancer with a 20% survival rate [1]. OAC patients receive neo-chemoradiotherapy prior to surgery [2]. Only 30% of patients achieve a pathological complete response to this treatment approach [3]. Hypoxia is present in most solid tumours and significantly contributes to treatment failure. Specifically, hypoxia specifically limits radiotherapy efficacy as oxygen is a potent radiosensitiser [4]. Increasing tumour oxygen level is a potential approach to improve radiosensitivity in OAC. Perfluorocarbons are chemically inert compounds which can dissolve large amounts of oxygen due to their chemical structure. This project aims to develop perfluorocarbon nanoemulsions (PFC-NEs) for intratumoural delivery of oxygen to reduce hypoxia and increase radiosensitivity in OAC.

Methodology

PFC-NEs were produced using lipoid, phosphate-buffered saline, and perfluorocarbons. PFC-NE stability was measured using Malvern's Zetasizer. Imaging capacity was measured using *ex vivo* mice livers via microCT. Oxygen-carrying capacity and release profiles were measured using a cell-based *in vitro* Seahorse assay. The toxicity of lead PFC-NEs were assessed using different *in vitro* and *in vivo* model systems. Following treatment of an isogenic model of OAC with PFC-NEs, clonogenicity, DNA repair, metabolism, cytokines, and cysteinyl leukotriene receptor expression were assessed.

Results

PFC-NEs are stable and can be visualised *ex vivo* using microCT. Lead PFC-NEs do not induce toxicity *in vitro* using different model systems. Formulation 001UG reduced zebrafish viability at 25%. Formulation 001UG significantly increases supernatant oxygen concentration and assimilates oxygen *in vitro* under normoxic conditions. Formulation 001UG also reduces the expression of HIF-1α under hypoxic conditions (0.5% O_2). Under normoxia, formulation 001UG significantly reduces clonogenicity basally, irrespective of oxygen-loading status. Formulation 001UG significantly reduces surviving fraction in combination with radiation. Under normoxia, formulation 001UG significantly increased SMUG1 expression basally. Formulation 001UG significantly reduces oxygen consumption rate and alters cytokine secretion in radioresistant OAC cells.

Conclusion

Hypoxia is a significant tumour microenvironmental factor which facilitates the selection of radiation resistant cancer cells. These data suggest that our novel PFC-NE functions as an oxygen delivery system with the potential to improve radiosensitivity in oesophageal adenocarcinoma.

References:

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