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Purpose or Objective

Evidence of the multiple effects of radiation on the molecular biology of prostate cancer cells is accumulating, but new frontier molecular biology is still required to achieve the personalisation of prostate cancer radiotherapy. We hypothesised that the induction of a radioresistant phenotype in response to fractionated radiation and exposure to an hypoxic environment share a common molecular response.

Material and Methods

A panel of 22Rv1 prostate cancer cells of differing radiosensitivities was developed through exposure to 60Gy in 2Gy dose fractions and exposure to 0.5% oxygen levels for 24 hours. The impact of these exposure on clonogenic survival to radiation was determined using clonogenic assays. The molecular response was examined through miRNA and high content Digiwest protein profiling technologies. Differentially expressed miRNAs and proteins were independently validated using RT-PCR, Western Blots and relationship with radioresistance was examined using clonogenic assays.

Results

Exposure to fractionated radiation significantly increased the clonogenic survival capacity of 22Rv1 cells, where compared to unexposed, wild type (WT) cells. The clonogenic survival of these cells was similar to that of hypoxic WT-22Rv1 cells. Three candidate miRNAs were associated with a radioresistant phenotype across the models: miR200a, miR210 and miR4284. Protein profiling identified 64 significantly differentially expressed proteins in RR22Rv1, when compared to WT-22Rv1 cells, including the androgen receptor, p53, YB-1, members of the Notch (Notch-1, Notch-3), apoptosis (bcl-xL) and DNA repair (PARP, ATR) signalling pathways. Interdependence between Notch-3, YB-1 and miR-4284 expression levels were identified though treatment with Notch, YB-1 and p53 inhibitors. These agents were associated with a modification in the clonogenic survival capacity of these cells following radiation exposure.

Conclusion

This study identifies a novel, therapeutically actionable, molecular network associated with radioresistance in prostate cancer.

OC-0382 Repurposing of FDA-approved drugs as novel radiosensitisers in hypoxic prostate cancer

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Purpose or Objective

Dose escalation radiotherapy in combination with androgen deprivation improves prostate cancer outcomes but despite this 30% of high risk patients experience early relapse. A reason for this failure is biological resistance to radiotherapy due to tumour hypoxia. In this study we used novel gene expression connectivity mapping software, QUADrATIC, to identify FDA approved drugs

that could be repurposed for the treatment of hypoxic prostate cancer.

Material and Methods

Prostate cancer hypoxia genes were identified using TCGA and RNA-seq analysis performed on prostate cell lines (PNT2-C2, PC3, LNCaP and DU145). A set of 66 hypoxia genes were the input for the QUADrATIC connectivity mapping software. Two drugs at the top of the ranking which were predicted to enhance radiation under hypoxia and one drug at the bottom of the ranking that was predicted to compromise the therapeutic benefit by enhancing hypoxic phenotype were selected. Clonogenic assays were undertaken, prostate cancer cells were treated with the selected drugs plus radiation under hypoxia and normoxia.

Results

Menadione and gemcitabine ranked highly as potential drugs that may target hypoxic tumour cells. Lisinopril was identified as drug that may be detrimental in patients with hypoxic tumour. Menadione decreased the surviving fraction of cells treated with radiation under hypoxia but had no effect on normoxic cells. Gemcitabine decreased the surviving fraction of cells treated with radiation under normoxia and hypoxia. Gemcitabine was a more effective radiosensitiser in hypoxia compared to normoxia.

Conclusion

Targeting tumour hypoxia in prostate cancer patients could enhance tumour radiosensitivity and improve patient response and outcomes. The QUADrATIC connectivity mapping software was used to identify FDA approved small molecule compounds which could be effective against hypoxic prostate cancer cells. Preliminary results have identified menadione and gemcitabine as potential radiosensitisers in the setting of hypoxic prostate cancer.

Proffered Papers: CL 7: Hematological Malignancies/Sarcoma/Palliation

OC-0383 Reduced cardiac risk in Hodgkin lymphoma patients treated with a full arc VMAT compared to b-VMAT

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Purpose or Objective

With the aim of assessing the dosimetric profile and the associated risk of developing second cancers and coronary artery disease (CAD), we tested two different volumetric arc therapy (VMAT) solutions, specifically optimized for mediastinal lymphoma presentations, among a cohort of patients treated with involved-site radiation therapy for mediastinal Hodgkin's lymphoma (HL).

Material and Methods

Thirty patients affected with mediastinal Hodgkin's lymphoma (15 males and 15 females) were included. Disease extent was mediastinum plus neck (n=10, 33%), mediastinum plus unilateral axilla (n=10, 33%) and mediastinum alone with bulky presentation (n=10, 33%). Prescription dose to the PTV was 30 Gy in 2-Gy fractions. The 'so-called' butterfly VMAT (b-VMAT) solution, consisting in non-coplanar multi-arcs, was compared with a full-arc VMAT (fa-VMAT; 360° coplanar plus a 60° non-coplanar VMAT arcs) approach. Lungs, female breasts, whole heart and heart sub-structures (coronary arteries,