

antagonizing SET could enhance the effects of RT against HCC. Using sub-G1 analysis, we showed that adding EMQA significantly increased RT-induced apoptosis of HCC cells. The number of tumor colony was also significantly decreased in HCC cells exposing to EMQA plus RT than either of the treatment alone. Lastly, using the PLC5 xenografted tumor model, the synergistic effects of SET antagonist combining RT were also observed.

Conclusion

SET is a novel oncoprotein that affects the radiosensitivity of HCC cells. A combination therapy with RT and the SET antagonist, such as EMQA, enhanced RT-induced apoptosis of HCC cells in vitro and in vivo.

PO-0987 Gemcitabine-based chemoradiotherapy gets improved with PARP inhibitor in pancreatic cancer cells
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Purpose or Objective

Pancreatic ductal adenocarcinoma (PDAC) is a devastating disease with a cumulative 5-year overall survival of less than 5% for all stages. Thirty percent of patients diagnosed with pancreatic adenocarcinoma present with a locally advanced disease and could benefit from chemoradiotherapy with gemcitabine, which is effective but toxic. Over the past few years, studies have focused on the development of targeted radiosensitizer such as poly(ADP-ribose) polymerase (PARP) inhibitor. We conducted this in vitro study to determine whether PARP inhibition enhances radiation-induced cytotoxicity of pancreatic adenocarcinoma.

Material and Methods

Pancreatic carcinoma cells, MIA PaCa-2 (BRCA1/2 wild-type), were treated with olaparib and/or gemcitabine and/or irradiation (2,5 and 10 Gy). In vitro cell viability, clonogenic assay, cell cycle distribution, γ -H2AX quantification, apoptosis and autophagy were assessed.

Results

In vitro, treatment with olaparib alone at 1 μ M was not cytotoxic but highly radiosensitized cells (standard enhancement ratio =1.23+/-0.02) and particularly at high dose per fraction (10 Gy). After 24 hours, the number of remaining γ -H2AX stained cells was higher when cells were treated with a combination of 10 Gy irradiation and olaparib compared to irradiation or olaparib alone. Furthermore, combination of olaparib and irradiation induced a G2/M arrest. In contrast, a non-cytotoxic concentration of gemcitabine could also radiosensitize cells, but clearly less than olaparib (SER=1.11+/-0.04). Radiosensitization by gemcitabine was associated with percentage of cells blocked in early S-phase just before irradiation. Finally, cell death quantification after 24 hours showed that none of the treatments induced apoptosis, whereas gemcitabine or 10 Gy irradiation alone induced autophagy.

Conclusion

Our results showed that MIA PaCa-2 cells could be radiosensitized with low dose of olaparib, through an increase of unrepaired double-strand breaks and a block in G2 phase. The radiosensitization was higher with high dose radiation. This may be translated into an enhancement of local control in vivo and better disease free survival. Investigations in three other pancreatic cells lines are in progress.

PO-0988 Following tumour microenvironment after Neoadjuvant radiotherapy with IVIM perfusion analysis
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Purpose or Objective

Neoadjuvant radiotherapy (NeoRT) improves tumor local control and facilitates tumor resection in many cancers. The timing between the end of the NeoRT and surgery is driven by the occurrence of side effects or the tumor downsizing. Some clinical studies demonstrated that the timing of surgery and the RT schedule influence tumor dissemination and subsequently patient overall survival. Previously, we developed a pre-clinical model demonstrating an impact of NeoRT schedule and the timing of surgery on metastatic spreading (Leroi et al. Oncotarget 2015). Here, we evaluate the impact of NeoRT on the tumor microenvironment by functional MRI (fMRI). We aim to identify non-invasive markers allowing to determine the best timing to perform surgery and avoiding tumor spreading.

Material and Methods

Based on our NeoRT model, MDA-MB 231 and 4T1 cells were implanted in the flank of SCID and BalbC mice, respectively. We locally irradiated tumors with 2x5Gy and then surgically removed at different time points after RT. Diffusion Weighted (DW) -MRI was performed every 2 days between RT and surgery. For each tumors we acquired 8 slices of 1 mm thickness and 0.5 mm gap with an "in plane voxel resolution" of 0.5 mm. For DW-MRI, we performed FSEMS (Fast Spin Echo MultiSlice) sequences, with 9 different B-value (from 40 to 1000) and B0, in the 3 main directions. We performed IVIM (IntraVoxel Incoherent Motion) analysis to obtain information on intravascular diffusion, related to perfusion (F: perfusion factor) and subsequently tumor vessels perfusion.

Results

With the MDA-MB 231, we observed a significant peak of F at day 6 after irradiation, this increasing is about 60% of the basal value (n=6, p<0,05). Moreover, D* parameters (also related to perfusion) increase at the same time. The other parameters of the DW-MRI, ADC and D presented no modification. We observed similar results with 4T1 cells, where F increased at day 3 (about 55%, n=10, p<0,05) then returned to initial level. The difference in timing for the peak of F (day 6 vs day 3) could be related to the difference in tumor growth according to the cell line (four weeks for MDA-MB 231 cells vs one week for 4T1cells). We performed surgery at the time of the F parameter peak in the MDA-MB 231 and we observed a decrease of the metastatic burden compared to surgery performed at day 4 or day 11 (absolute number of metastasis 23 VS 1 VS 8 with n=4).

Conclusion

For the first time, we demonstrate the feasibility of repetitive fMRI imaging in preclinical models after NeoRT. With these models, we show a significant difference in perfusion-related parameters (D* and F) at a specific time point depending of the tumor cells. These modifications are correlated to a decrease of metastasis spreading related to the surgery procedure. These results open new perspectives in the personalized medicine and MRI guided surgery timing after NeoRT.

PO-0989 Sub-lethal radiation allows an efficient antitumor therapy with engineered T-cells in RIP-Tag2 mice

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