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Oxidative and inflammatory effects in normal tissues of mice exposed whole body to combined treatments with conventional radiotherapy or protontherapy and a PARP inhibitor

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This work belongs to the ToxIP3 program which aims to assess toxicity to healthy tissues of protontherapy versus photontherapy and their combination with a PARP inhibitor: olaparib. PARP inhibitors have a recognized radio-sensitizing effect by causing an increase in unrepaired DNA breaks after irradiation. However, their toxicity in association with irradiation has not yet been adequately studied *in vivo.*

For this purpose, C57Bl6 mice were whole-body irradiated with photon or proton beams +/- olaparib. Survival was stronger decreased after protons than after photons. Olaparib did not modify the survival or the weight of unirradiated mice but strongly decreased them when associated to irradiation. Blood and various organs were collected after the onset of acute toxicities. Skin, brain, lung, heart, small intestine and liver were cryomilled and biomarkers of genotoxicity, oxidative stress and inflammation were measured. Genotoxicity, measured by 8-oxodG level in lymphocytes, was significantly increased only after photon irradiation. PARP1 activity was also increased in all organs only after photons and the addition of olaparib decreased it. Moreover, olaparib caused oxidative damage to lipids (malonedialdehyde level) and proteins (carbonyls level) varying according to the tissues with an inverse effect when combined with photons or protons. The level of plasma inflammatory cytokines was increased after photons or protons. Olaparib decreased TNF-α, IFN-γ, but also IL-10, and increased IL-6 and IL-12p70.

In conclusion, protons leaded to: an increase in acute toxicity compared to photons (mouse survival and weight, PARP1 activity) but a decrease in oxidative damage to lipids, proteins and DNA in the majority of tissues. The combination with olaparib leaded to an increase in acute toxicity (survival, weight, PARP1 activity, pro- and anti-inflammatory cytokines) but also to a decrease in other pro-inflammatory cytokines and in oxidative damage to lipids (after photons only). This study will enable the clinical use of olaparib associated with photon or proton beam radiotherapy.

Keywords:
Irradiation; normal tissues; PARPi; genotoxicity; inflammation.