Treatment efficacy modelling combining anti-PARP1 Olaparib® and fractionated irradiation on 3D Triple-Negative breast cancer cultures.

Clémence Dubois1,2, Fanny Martin3, Chervin Hassel4, Antoine Goisnard2, Pierre Dauma5, Corinne Aubel1, Emmanuelle Mouneout6, Frédérique Penault-Llorca7,8 & Mahdih Bardad9

1 - Université Clermont Auvergne, Centre Jean Perrin, INSERM, U1240, Imagerie Moléculaire et Stratégies Thérapeutiques, F-63000 Clermont Ferrand, France.
2 - Université Clermont Auvergne, Institut Universitaire de Technologie, INSERM, U1240, Imagerie Moléculaire et Stratégies Thérapeutiques, F-63000 Clermont Ferrand, France.
3 - Département de Radiothérapie, Centre Jean Perrin, F-63000 Clermont Ferrand, France.
4 - CHU Purpan, Centre de Physiopathologie de Toulouse Purpan, INSERM, UMR 1043 / CNRS UMR 5282, Antigen Presenting Cells and CD4 T cell responses, F-31024 Toulouse, France.
5 - Université Clermont Auvergne, Faculté de Médecine, INSERM, U1240, Imagerie Moléculaire et Stratégies Thérapeutiques, F-63000 Clermont Ferrand, France.

The “Triple-Negative Breast Cancer” (TNBC) subtype is particularly aggressive and of poor prognosis. To improve the patient outcome, targeted therapies such as Poly-ADP-ribose Polymerase inhibitors (anti-PARPs) were developed in preclinical and clinical studies [1]. Thus, in order to improve their efficacy, PARP1 inhibitors may be used in combination with radiotherapy (Rx), as both strategies aim to increase the number of lethal DNA double-stranded break in tumour cells.

In this study, the effectiveness of a treatment combining the anti-PARP1 Olaparib® (low and high doses) and fractionated irradiation (2 Gy / day) was studied on two TNBC models cultured in 2D and 3D condition (spheroids), which mimics the tumour microenvironment.

Method

DNA double strand-breaks induction

FOC gammaH2AX immunofluorescent staining and quantification after treatment with Olaparib for 4h combined to 2 Gy irradiation.

Clonogenic repopulation

Clonogenic survival after a treatment with Olaparib alone for 24h, 72h or 128h (A), or combined with fractionated radiotherapy of 5 or 10 Gy (B).

Cell survival

The Sulforhodamine B survival test was carried out on TNBC cells after a treatment with Olaparib alone for 24h, 72h or 128h or combined with fractionated radiotherapy of 5, 10 or 15 Gy. The data from both cell lines were analyzed by an ANOVA.

Transcriptomic in silico analysis

Analysis of the Differently Expressed Genes (DEG) between SUM1315 and MDA-MB-231 cell lines. All the analyzed genes are implicated in the DNA repair pathways or are biomarkers of anti-PARP efficacy.

Conclusion & Perspectives

These works led to the promising perspective of a (i) daily (ii) low dose and (iii) long-term Olaparib administration coupled to fractionated radiotherapy on resistant metastatic breast cancers, and possibly for oligometastatic brain localizations, given the very difficult handling of these advanced stages.

Funding: these works were supported by a national funding from Ligue Contre le Cancer under the project name « PinkMind ». 

References

[1] In this study, the effectiveness of a treatment combining the anti-PARP1 Olaparib® (low and high doses) and fractionated irradiation (2 Gy / day) was studied on two TNBC models cultured in 2D and 3D condition (spheroids), which mimics the tumour microenvironment.