BIOLOGICAL EFFECTS IN GLIOBLASTOMA STEM CELLS AFTER CHARGE-PARTICLE IRRADIATION: HADRONTHERAPY AS A NEW THERAPEUTIC OPPORTUNITY?

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Glioblastoma multiforme (GMB) is the most common type of malignant primary brain tumor in adults. Despite the treatments with established therapies as surgery, radiation therapy and concomitant adjuvant chemotherapy with temozolomide, the median survival is still in the range of just 12 months. The high recurrence rate and failure of conventional treatments can be explained by a recent cancer model that assumes the presence of stem cells inside the tumour mass having a greater resistance to standard therapeutic approaches. In this context, there is much interest in elucidating the mechanisms of resistance to radiation therapy and developing novel, more effective approaches.

Some literature data report that glioma stem cells (GSCs) promote radioresistance to gamma rays by preferential activation of the DNA damage response followed by a better capability to repair DNA damage. Moreover, recent experimental evidence showed a higher effectiveness of carbon ions respect to photons in inactivating cancer stem cells from colon carcinoma, likely related to the different quality of the induced DNA damage. These results suggest a potential advantage of Hadrontherapy (that use external beams of charged particles) compared with conventional radiotherapy. Clinical trials already started at the Hidelberg Ion-beam Therapy Center (HIT) with promising results.

In order to investigate the mechanisms involved in the molecular and cellular response of GSC to ionizing radiations, we irradiated two GSC lines (namely #1 and #83), derived from patients with different clinical outcome, with 137Cs photons at the Istituto Superiore di Sanità, Rome, and with protons or carbon ions with energy of about 62 MeV/u at the Laboratori Nazionali del Sud LNS-INFN, Catania. The dose range was 1-40 Gy. The biological effects investigated have been DNA damage and repair, cell cycle progression and cell death as measured by flow cytometer and clonogenic survival assay, respectively.

The results so far obtained show some differences in the radiation response depending on the cell line and radiation type. In particular, when compared to photons, charged particles, especially C-ions, seem to be more effective in inactivating GSCs, as pointed out by the clonogenic analysis. This can be related to the different quality of the induced DNA damage, highlighting a potential advantage of Hadrontherapy in glioblastoma patients. Further experiments are in progress to consolidate data and to get more insights on the relationship among the different end points investigated at molecular and cellular level.

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