

DAGROSA-1: Radiobiological studies of BNCT to thyroid carcinoma

Maria Alejandra Dagrosa and Mario Pisarev

*Dept. Radiobiologia
Centro Atómico Constituyentes (CNEA)
Av. Gral. Paz 1499, B1650 Villa Maipú, Buenos Aires, Argentina
dagrosa@cnea.gov.ar*

Poorly differentiated (PDTC) and anaplastic thyroid carcinomas (ATC) are relatively rare tumors that also arise from follicular cells and are associated with aggressive disease. Both are refractory to radioiodine, and traditional chemotherapy or radiotherapy having a limited benefit. Boron neutron capture therapy (BNCT) is an option for selective binary treatment of local tumors. Previously we have performed in vitro and in vivo studies in order to apply BNCT to PDTC and ATC. Two boron compounds, boronophenylalanine (BPA) and tetrakis-carborane carboxylate ester of 2,4-bis-(a, b-dihydroxyethyl)-deuteroporphyrin IX (BOPP) were evaluated alone and combined, showing a complete regression for smaller tumors and a growth inhibition for larger tumors for a period of a month. More recently we began to analyze the DNA damage response (DDR) induced by BNCT in thyroid tumor cells. It is known the radiation field produced in the tumor during the application of BNCT is a mixture of high and low LET components which activates the DDR including double strand break (DSB) repair and cell death by mitotic catastrophe or apoptosis. The description of these mechanisms would allow manipulating the response of the thyroid cell, increasing the radiosensitivity of the tumor cells to the therapy. In our first studies we showed that BNCT produces larger and more complex chromosome aberrations (micronuclei) than conventional radiotherapy. Also, we analyzed γ H2AX foci frequencies and their size on the one hand, and the expression of main effector enzymes of non-homologous end joining (NHEJ) or by homologous recombination repair (HRR) mechanisms in thyroid follicular carcinoma cells (WRO). We performed the same measurements using gamma radiation and the melanoma human cell line (Mel J) in order to compare the results with a standard radiotherapy and another type of carcinoma. Cells were irradiated at the thermal column of the RA-3 reactor (Ezeiza Atomic Center), with a thermal flux near to $(1.0 \pm 0.1) 10^{10} \text{ n cm}^{-2} \text{ s}^{-1}$. These findings were consistent with an activation of HRR mechanism in thyroid cells by BNCT. Melanoma cells showed different DNA damage pattern and the activation of both repair pathways (HRR and NHEJ). The results obtained by our team allowed us to demonstrate that DDR is tumor specific and highlighted different blocking points that could enhance the damage caused by BNCT. In this way, two molecules described as repair inhibitors, were analyzed as possible radiosensitizers. The first one, a specific inhibitor of the enzyme Rad51: (E) -3-benzyl-22- (pyridin-3-yl) vinyl quinazolin-4 (3H) -one (B02), and the other, a non-specific inhibitor of repair enzymes such as sodium butyrate (NaB), a histone deacetylase inhibitor (HDACI). The last mechanism studied as a part of the DDR produced by BNCT in tumor cells, was the pathway TGFbeta/Smad and crosstalk between members of the different vias that are part of the DDR. Preliminary studies showed that this via is active increasing the genetic instability which would result in a greater number of chromosomal aberrations and cell death. In conclusion we believe that the description of the cellular mechanisms activated by BNCT will allow us to study strategies for manipulating the cellular response with possible translation to the clinic.