A BRAIN METASTASIS THERAPY TWEAK, FOR THE BETTER? CONCOMITANT STEREOTACTIC RADIOTHERAPY & MOLECULAR-TARGETED THERAPY

Dr Manuel Sarmiento Dr James R. Larkin Ms Kleopatra AndreouMs Christina Simoglou Karali Prof Nicola R. Sibson

Abstract

Manuel Sarmiento Soto, James R. Larkin, Kleopatra Andreou, Ana Dominguez Bajo, Christina Simoglou Karali and Nicola R. Sibson. Cancer Research UK & Medical Research Council Oxford Institute for Radiation Oncology, Department of Oncology, University of Oxford, UK. The most common cause of cancer demise is the metastasis to distant organs. In particular, brain metastasis represents one of the highest mortality rates in the oncology field. Some of the reasons for the meagre advance in the treatment of this disease are the limited conditions for favourable surgical debulking of tumour, off-target effects of conventional treatments and the limited efficacy of delivery into the brain for currently available drugs. Contrary to those conventional strategies, targeted anticancer therapies exploit molecules that act on specific mechanisms that may disturb the malignant process, whilst minimising adverse effects on healthy tissues. Based on that approach, we have been working on novel anti-cell adhesion molecule (CAM) therapies. Our approach has shown notable reductions in brain metastasis growth [1] and a marked reduction in associated neuro-inflammatory processes (Soto MS et al 2016, in press). Here we report studies in which we have further tested this strategy in combination with focal brain radiotherapy and, strikingly, have shown opposite effects on metastatic growth depending on the CAM target (either LFA-1 or ALCAM). SCID female mice were intracerebrally injected with 5x103 MDA231Br-GFP (human metastatic breast carcinoma) cells, either in the parental form or following siRNA knockdown of either LFA-1 or ALCAM (n=12/group). At 2 weeks after brain metastasis induction, half of the mice in each group received a single dose of focal radiotherapy (1x15Gy). One week later, mice were sacrificed and tumour volume quantified. Mice injected with either LFA-1 or ALCAM knockdown MDA231BR-GFP cells showed a significant reduction (70% or 85%, respectively; $p<0.01$) in tumour volume compared to those injected with

parental MDA231BR-GFP cells. At the same time, a >3-fold reduction in tumour volume was observed in mice injected with parental MDA231Br-GFP cells followed by focal irradiation compared to non-irradiated mice. However, a further significant reduction in tumour volume was found in irradiated mice compared to non-irradiated mice injected with the LFA-1 knockdown tumour cells. In contrast, mice injected with ALCAM knockdown cells showed a significant increase in tumour re-growth compared to non-irradiated mice (Figure 1). These data suggest a significant role for both LFA-1 and ALCAM during tumour progression. However, whilst a potential synergy between anti-LFA-1 therapy and radiotherapy is indicated, combination of anti-ALCAM therapy with radiotherapy appears to be prohibited. It is well known that CAMs give different grades of resistance and susceptibility to cancer cells against radiation. This work shows the potential of anti-CAM therapy for brain metastasis either alone or in combination with radiotherapy, but demonstrates the need for caution with regards to specific combinations of these therapies.

1. Soto MS, Serres S, Anthony DC and Sibson NR. Functional role of endothelial adhesion molecules in the early stages of brain metastasis. Neuro-oncology. 2014; 16(4):540–551.