Contribution of an oxygen effect to the radiosensitization of anti-inflammatory agents: EPR and DCE-MRI studies

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Introduction:

In the last few years, the combination of cyclooxygenase-2 (COX-2) inhibitors and radiotherapy has been widely investigated (1-4). The suggested mechanisms by which COX-2 inhibitors enhance tumor response to radiation are the following: increased susceptibility to radiation-induced apoptosis, cell cycle redistribution, and inhibition of repair from sublethal radiation damage. We made the hypothesis that an oxygen effect may also contribute to the radiosensitivity of COX-2 inhibitors. Our assumption was that an anti-inflammatory agent may increase the tumor oxygenation by a decrease in the recruitment of leucocytes and macrophages that consume oxygen at high rate.

Materials and Methods:

Two types of mice tumors were used in this study: FSaII and TLT tumors implanted in the gastrocnemius muscle of mice. Anti-inflammatory agents : Diclofenac (IP 20mg/kg), Piroxicam (IP 25mg/kg), Indomethacin (IP 2mg/kg) and Hydrocortison (IP 7.5mg/kg) and a selective COX-2 inhibitor NS-398 (IP 10mg/kg). Oxygen pressure (measured by EPR oximetry with a 1.2 GHz spectrometer, Magnettech, Germany) and blood flow (monitored with DCE MRI at 4.7 Tesla) were monitored in the tumor when the diameter reached 8 +/-0.5 mm. The tumor was irradiated using an RX irradiator (Philips medical, 250 kV, 1.2 Gy/min) to a total dose of 18 Gy.

Results:

All anti-inflammatory agents induced an increase in tumor pO2. Fig 1 shows the increase in tumor pO2 after NS-398 administration in two tumor models.

DCE MRI studies carried out after NS-398 indicated that the increase in tumor oxygenation is not due to an increase in tumor perfusion. At the time of maximal reoxygenation, we found that the percentage of perfusion (region were the contrast agent could flow in i.e. characterized by significant values for Ktrans and/or vp) was decreased, that the permeability (Ktrans) was decreased, and that the volume plasmatic fraction (vp) was unchanged (Fig 2). These results are in accordance with other perfusion measurement realized with laser Doppler techniques.

Finally, we observed a longer regrowth delay when irradiation was made 30 min after injection of NS-398 than using radiation alone (Fig 3).

Discussion

NS-398 induced a increase in tumor oxygenation. Since this increase is not due to an increase in blood supply, it is likely that an effect on oxygen consumption is involved. At the time of increase in pO2, there was an increase in the regrowth delay after irradiation, suggesting that the radiosensitization may be due to an oxygen effect. Histological studies are in progress to confirm the decrease in the recruitment of inflammatory cells.

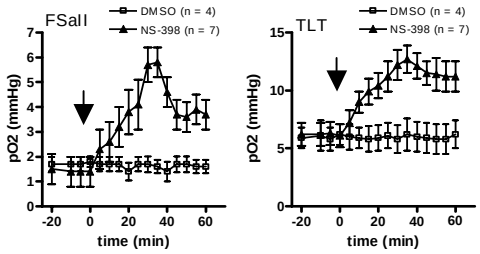

Figure 1: pO_2 (mmHg) (Mean +/- SEM) measured by EPR oximetry before and after NS-398 injection or DMSO (vehicle)

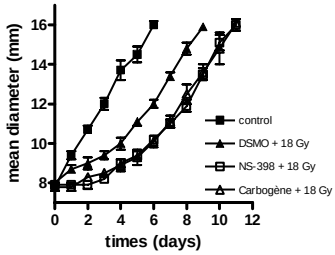

Figure 3: Regrowth delay on 4 groups FSaII tumors : control, RX+DMSO, RX+NS-398, RX+carbogen

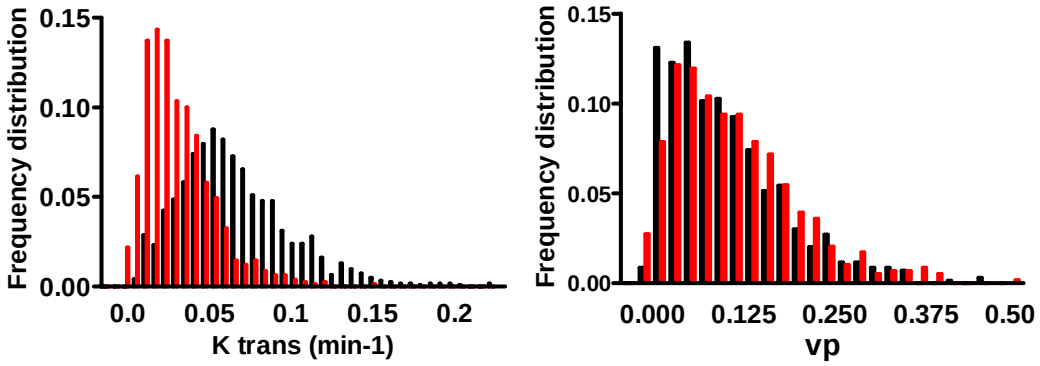

Figure 2: DCE MRI :
Right : Pooled histogram of Ktrans factor (permeability) before(black) and after NS-398 treatment (red).
Left : Pooled histograms of vp factor (plasmatic volume fraction) before (black) and after NS-398 treatment (red).

References:

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