Changes in the tumor microenvironment early after treatment with the anti-angiogenic agent thalidomide

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Introduction:

Tumor angiogenesis is a well known process allowing tumor expansion. But the new formed blood vessels are immature and present some structural and functional abnormalities (1) which can hinder therapeutic effectiveness (2). Up to now, antiangiogenic treatments were used to suppress tumor vascular supply and then starve tumor from oxygen and nutrients (3). Recently, R.K. Jain hypothesized that tumor vasculature could be normalized in the early stage of an anti-angiogenic treatment by pruning the immature and inefficient blood vessels (4). This would lead to a transient improvement of tumor oxygenation and to a better radiotherapy co-treatment efficacy. At present time no or very few studies have been made about the characterization of tumor micro-environment in this early time (5-6). The present study characterizes FSAII tumor environment early after thalidomide treatment and determines the optimal time-scale for combining such treatment with radiotherapy.

Materials and Methods:

FSAII bearing mice were used. Treated mice received daily 100 µl i.p. thalidomide injection (200mg/kg) and control mice received 100µl i.p. vehicle alone (DMSO). Oxygen pressure (pO_2) was measured daily by EPR oximetry with a 1.2 GHz spectrometer (Magnettech, Germany). To estimate tumor perfusion, DCE MRI (4.7 Tesla, Bruker Biospec,T1GRE sequence) was performed using P792 as contrast agent. Only tumor voxels showing a typical signal enhancement, selected after a power spectrum and a cluster analysis, were used for the pharmacokinetic analysis. For this analysis, a Su and Nalcioglu model (7) was used to extract D0(mM) which is proportional to the plasma volume fraction and D1 (mM/min) which is proportional to the permeability. In addition, Patent Blue Staining (Patent blue 1.25%) and Laser Doppler imaging were also realized. A wick-in-needle technique (Stryker) was performed to estimate interstitial fluid pressure (IFP). A regrowth delay experiment was realized after a single dose irradiation of 20 Gy (Phillips medical, 250 kV, 1.2 Gy/min).

Results:

Daily thalidomide treatment modified tumor pO_2 with a significant ($p<0.05$) maximum increase at day two (Fig.1). At this day, using DCE-MRI concomittent with power spectrum and cluster analysis, we observed a significant decrease ($p<0.05$) in the number of perfused voxels from 73.3±8.1% to 42.1±9.73% for control and treated group respectively. Among those voxels, the perfusion was improved for thalidomide group but no significant difference was shown about the permeability. The increase in tumor perfusion at day 2 was confirmed by laser-doppler imaging and patent blue staining.

At day 2, the IFP was significantly decreased for thalidomide group (15±0.89mmHg vs 19±0.62mmHg, $p<0.01$) (Fig.2).

Without irradiation, the regrowth delay for thalidomide and control group was not different. But, with irradiation, the regrowth delay was increased by a factor 1.7 for the thalidomide treated group compared to the irradiated group without co-treatment (Fig.3) .

Discussion

This study demonstrated that tumor microenvironment parameters fluctuate during anti-angiogenic treatment. This is of crucial importance to determine the optimal time scale to combine treatments. In fact, our results show a better radiosensitivity after two days of thalidomide treatment resulting from an increase in pO_2 due to an improvement of perfusion. This could be the consequence of the IFP decrease resulting from the immature vessels pruning.

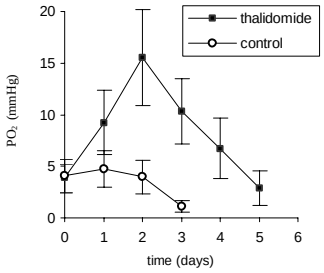

Fig.1 Effect of daily thalidomide treatment on FSAII tumor pO_2 .

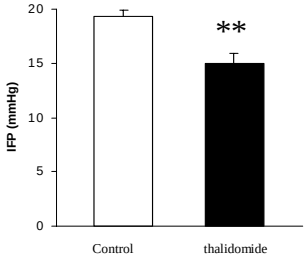

Fig.2 Effect of thalidomide after two days of treatment on FSAII tumor IFP.

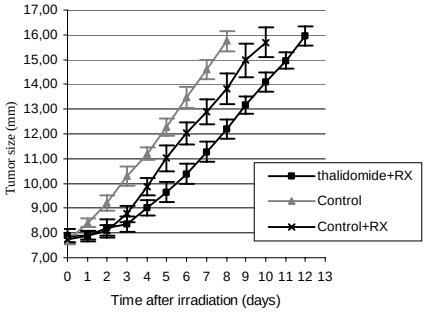

Fig.3 Regrowth delay after a single dose of 20 Gy : control vs 2 days of treatment with thalidomide

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