Changes in the tumor micro-environment induced by xanthinol nicotinate: characterization of the hemodynamic parameters and their consequences for cytotoxic therapies

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Introduction:

Structural and functional abnormalities in the tumor vascular network are factors of resistance of solid tumors to cytotoxic treatments. New strategies for transiently opening the tumor vascular bed to alleviate tumor hypoxia (source of resistance to radiotherapy) and improve the delivery of chemotherapeutic agents are needed.

Objectives

We hypothesized that xanthinol nicotinate (XN), a vasodilator used in the management of peripheral and cerebral vascular disorders, could improve tumor perfusion and oxygenation in order to get a better radiotherapy and chemotherapy outcome.

Materials and Methods:

TLT tumors were implanted in the gastrocnemius muscle of mice. Oxygen pressure (measured by EPR oximetry with a 1.2 GHz spectrometer) and blood flow (monitored with DCE MRI at 4.7 Tesla, using P-792 as contrast agent) were monitored in the tumor before and after treatment by XN (IP, 75 mg/kg). To assess the potential benefit of the oxygen effect on radiotherapy, tumors were irradiated using a X-Rays irradiator (10 Gy). The effect on chemotherapy was assessed by injecting suboptimal dose of cyclophosphamide (50 mg/kg).

Results:

Tumor pO2 increased rapidly after XN administration, with maximal pO_2 values obtained 10 to 30 minutes after administration (Fig 1). Hemodynamic parameters indicate that Vp and Kep were significantly increased after XN administration (Fig 2). The efficacy of both radiotherapy and chemotherapy treatments was improved after XN pre-treatment (Table 1 and 2).

Discussion :

The administration of XN significantly contributes to the increase in efficacy of cytotoxic treatments. In vivo EPR and DCE-MRI are helpful in identifying the dynamic changes in the tumor micro-environment to optimize the administration schedule.

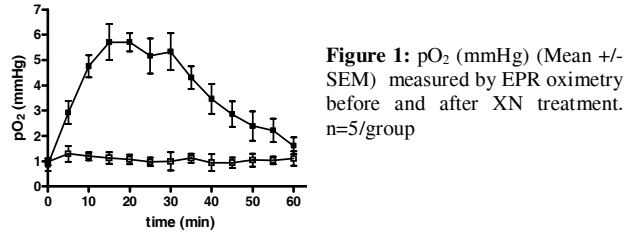

Figure 1: pO_2 (mmHg) (Mean +/- SEM) measured by EPR oximetry before and after XN treatment. n=5/group

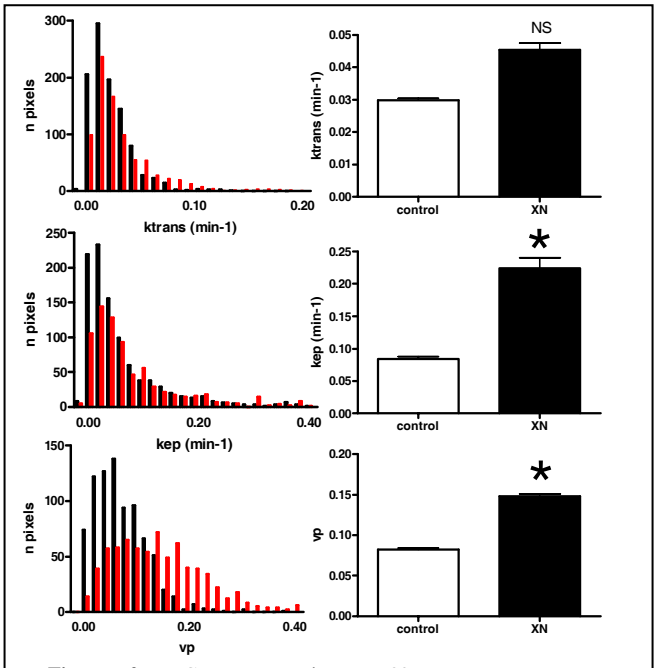

Figure 2: DCE MRI using P-792 as contrast agent. Hemodynamic parameters in control and XN-treated mice.

Groups	Time to 14 mm (days)	Regrowth delay (days)
saline	6.16 ± 0.25	
Xanthinol	6.68 ± 0.73	ns
saline + 10 Gy	10.39 ± 0.50	4.23 ± 0.75
Xanthinol + 10 Gy	12.48 ± 0.28	5.80 ± 1.01

Table 1: Potentiation of radiotherapeutic effect.
Regrowth delay of 4 groups of TLT tumor groups. N=5/group

Groups	Time to 14 mm (days)	Regrowth delay (days)
saline	6.16 ± 0.25	
Xanthinol (XN)	6.68 ± 0.73	ns
Cyclophosphamide	7.81 ± 0.69	1.66 ± 0.94
XN +Cyclophosphamide	12.29 ± 0.92	4.48 ± 1.61

Table 2: Potentiation of chemotherapeutic effect.
Regrowth delay of 4 groups of TLT tumor groups. N=5/group