Adapting tumor Interstitial Fluid Pressure for intraperitoneal chemotherapy.

Félix Gremonprez; Andrei Izmer; Frank Vanhaecke; Christian Vanhove; Piet Pattyn; Wim Ceelen

Ghent University Hospital, Ghent, Belgium

Background

The raised interstitial fluid pressure (IFP) in tumors hinders the penetration and uptake of cytotoxic drugs. Reduction of the IFP by anti-VEGF and/or anti-PDGFR therapy enhances delivery of systemic chemotherapy. It is unknown, whether these effects could also enhance intraperitoneal chemotherapy (IPC).

Methods

Bilateral subperitoneal injections of 1.5 x 10^6 HT-29 cells in 40 µl Matrigel were administered to Foxn1^{nu} nude athymic mice (Harlan). On day 10 to 15, mice were administered either placebo, Imatinib (50 mg/kg daily), Pazopanib (100 mg/kg daily), or Bevacizumab (5 mg/kg 2x). At day 15, each mouse underwent an open IPC procedure with 150 mg/m² Oxaliplatin for 60' at 37°C. Intraoperative measurements of tumor IFP (Samba Preclin®) and pO_2 (Oxylite®) were performed. Tumor, blood, and perfusate samples were taken postoperatively. A second experiment made use of DCE-MRI on day 14, 19 and 26 to assess tumor growth and microvascular permeability.

Results

Tumor IFP was significantly lower in the Bevacizumab and Pazopanib groups. Interestingly, the hypoxic fraction (pO_2 <5 mmHg) was also significantly increased in the Bevacizumab group. Tumor size and blood Pt concentration did not differ. Tumor growth was delayed mainly in the Bevacizumab and Pazopanib groups.

Conclusions

Treatment with Bevacizumab and Pazopanib leads to a markedly reduced IFP in colorectal xenograft tumors. This effect may allow for deeper penetration and higher concentration of Oxaliplatin in peritoneal tumors. The increased tumor growth delay confirms the potential of possible combination therapy. IHC, Pt (LA-ICP-MS) and DCE-MRI (Mistar) analysis are currently ongoing.