Pharmacological modulation of tumor interstitial fluid pressure (IFP) to enhance intraperitoneal chemotherapy (IPC).

Gremonprez F.[1]; Izmer A.[2]; Vanhaecke F.[2]; Descamps B.[3]; Vanhove C.[3]; Pattyn P.[1]; Ceelen W.[1]

[1]: *Laboratory of Experimental Surgery, Department of Gastrointestinal surgery, Ghent University Hospital, Ghent, Belgium*
[2]: *Atomic and Mass Spectrometry, Department of Analytical Chemistry, Ghent University, Ghent, Belgium*
[3]: *Infinity (iMinds-IBiTech-MEDISIP), Department of Electronics and Information Systems, Ghent University, 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 MRI (T2) on day 14, 19 and 26 to assess tumor growth. In addition to the previously described groups, a sham group was included that did not receive oxaliplatin or pretreatment. DCE-MRI with Vistarem® (Guerbet) was also performed to determine tumor microvascularity and pretreatment effect.

Results

Tumor IFP was significantly lower in the Bevacizumab and Pazopanib groups (p<0,001). Interestingly, the hypoxic fraction (pO_2 <5 mmHg) was also significantly increased in the Bevacizumab group (p=0,026). Tumor size and blood Pt concentration did not differ. Pt/P ratio (Oxaliplatin) was increased up to 2-3x in the tumor borders after Bevacizumab and Pazopanib treatment. Tumor growth was delayed mainly in the Bevacizumab and Pazopanib groups (p=0,0006).

Conclusions

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