ANTIANGIOGENIC AND ANTITUMOUR EFFECTS OF METRONOMIC IRINOTECAN (CPT-11)

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Background. Metronomic antiangiogenic chemotherapy is the chronic administration of chemotherapy at relatively low, non-toxic doses on a frequent schedule of administration (e.g. daily) continuously or with no prolonged drug-free breaks. **Aims**. *In vitro* assessment of the anti-endothelial effect of continuous low concentrations of SN-38 (the active metabolite CPT-11), for prolonged periods of time (144h); investigation of the relationship between expression, synthesis and secretion of pro- and anti-angiogenic factors in human normal and tumor cell lines after metronomic administration of SN-38; *in vivo* assessment of the antitumour efficacy of metronomic CPT-11. **Methods**. *In vitro* human endothelial cells (HMVEC-d and HUVEC) and colorectal cancer cell lines (SW620 and HT-29) were treated both at low and high concentrations using a continuous (144 h) drug exposure protocol to evaluate the antiproliferative effects (expressed by experimental IC_{50}s), the inhibition of modulation of gene expression of pro- (vascular endothelial growth factor, VEGF) and anti-angiogenic (trombospondin-1, TSP-1) factors by real time-PCR. Nude mice with s.c. HT-29 xenografts were administered with metronomic CPT-11, or with CPT-11 at the maximum tolerated dose (MTD). **Results**. *In vitro* SN-38 inhibited selectively the proliferation of HMVEC-d and HUVEC (IC_{50}=0.014±0.0024 and 0.21±0.029 nM, respectively; mean±SD). The IC_{50} of the colorectal cancer cell line SW620 and HT-29 were 0.64±0.014 and 1.5±0.05 nM, respectively. The expression of TSP-1 gene was greatly increased in endothelial cells treated at the IC_{50} (143.4% *vs*. 100% of control for HUVEC and 249.8% *vs*. 100% of control for HMVEC-d), whereas the expression of VEGF was different in the two cell lines (62.6% *vs*. 100% of control for HUVEC and 133.7% *vs*. 100% of control for HMVEC-d). The *in vivo* therapeutic effect of CPT-11 metronomic regimen (4 mg/kg/day) after 47 days was significant (24.65% *vs*. 100% of controls, $P<0.05$), MTD CPT-11 (100 mg/kg once weekly), as expected, inhibited the tumour growth (9.7% *vs*. 100% of controls, $P<0.05$). However the toxicity profile was highly favourable for metronomic regimen, whereas the MTD CPT-11 treated animals showed a significant weight loss, requiring supplementary subcutaneous saline injections during the entire study. **Conclusions**. *In vitro* results show the antiangiogenic properties of low doses SN-38, suggesting the possible role of TSP-1 in this effect. *In vivo* the CPT-11 metronomic schedule is effective against colorectal cancer without toxic effect on mice.