IRINOTECAN METRONOMIC CHEMOTHERAPY IN METASTATIC COLORECTAL CANCER PATIENTS: A PHARMACOKINETIC AND PHARMACODYNAMIC STUDY

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Background. Truly long-term, regular frequency, low-dose chemotherapy (metronomic/antiangiogenic chemotherapy) has been recently developed but is still uncommon in adult oncology. Metronomic irinotecan (CPT-11) clinical trials for treatment of cancer has not been reported and pharmacodynamic (PD) and pharmacokinetic (PK) investigations have not been yet performed. **Aims.** The experimental hypothesis to be tested is whether CPT-11 metronomic regimens are feasible and effective, investigating the pharmacokinetic of CPT-11 and SN-38 (the active metabolite), the modulation of pro- (VEGF) and anti-angiogenic factor (thrombospondin-1, TSP-1) expression and establishing possible significant relationships among clinical, PK and PD parameters. **Patients and methods.** Twenty consecutive patients (M/F, 11/9; age range, 51-79 years) with a diagnosis of metastatic colorectal carcinoma, treated with previous palliative chemotherapy with fluoropyrimidines, oxaliplatin and irinotecan were studied. The doses of CPT-11 administered as 63-day protracted continuous infusion, with no interruption, for each group of patients were as follows: CPT-11 1.4 mg/m^2/day (*n*=7), CPT-11 2.8 mg/m^2/day (*n*=5), CPT-11 4.2 mg/m^2/day (*n*=8). Toxicities were scored according to NCI criteria. Drug levels were examined by HPLC, whereas plasma levels of TSP-1 and VEGF were evaluated by ELISA. **Results.** Four patients (20%) obtained a stable disease despite the tumour resistance to CPT-11. This stabilization of disease lasted a median period of 3.9 months (range, 3 to 5 months). In the remaining 16 patients (80%) a progression was observed. Toxicities ≥ grade 1 were not observed. Three (15%) and five patients (25%) experienced, respectively, a transitory grade 1 diarrhea and grade 1 nausea, resolved without interrupting the treatment. Hematological toxicity was not observed. The low, but measurable, levels of plasma CPT-11 and SN-38 reached the C_{max} of 277.6±125.3 ng/ml and 1.62±0.45 ng/ml (mean±SD), respectively, at the lowest CPT-11 dose. The antiangiogenic effect of metronomic CPT-11 seems to be suggested by the TSP-1 plasma concentrations that were increased at the CPT-11 1.4 and 2.8 mg/m^2/day schedules (e.g. at day 49, 153.4±30.1% and 130.4±9.2% *vs.* 100% of baseline values before treatment, respectively) and by the initial, but variable, increase in plasma VEGF (e.g. at day 21, 124.4±41.7% and 132.3±46.8%, respectively) probably due to the induced hypoxic conditions of tumour. Interestingly, the SN-38 plasma concentrations were statistically related to TSP-1 plasma levels in the 4 patients with stable disease (*P*=0.0062, r=0.3995). **Conclusions.** Metronomic CPT-11 schedules are feasible, very well tolerated and clinically considerable in 20% of CPT-11 resistant patients. Plasma SN-38 concentrations were measurable and related to the increase of the antiangiogenic factor TSP-1.