5-Fluorouracil (5-FU) and Irinotecan (CPT11) are widely used in colorectal cancer (CRC) in regimens including bolus/infusional 5-FU, folinic acid modulation and CPT11 (FOLFIRI), as well as targeted monoclonal antibodies, such as cetuximab. This controlled phase II study in a population of resectable metastatic CRC aimed to perform individual dose adjustments in order to safely increase the dose of both 5-FU and CPT11, improving efficacy without affecting tolerance (low toxicity profile).

**METHODS:**

5-FU tailored therapy: the large variability of 5-FU metabolism is related to impaired DHprymidine Dehydrogenase (DPD) activity. Patients with DPD deficiency can experience early-onset severe (25%), even fatal (0.3%) toxic side effects. This deficiency can be detected before chemotherapy by using a screening based on a multiparametric approach (5-FU<sub>LODPM</sub>™, Angers, France) that takes into account polymorphisms on the DPDY gene (Fig. 1), indirect DPD activity (levels of uracil, dihydouracil and dihydriouracil/uracil ratio - Fig. 2), and patient characteristics. This screening for DPD activity, when used in conjunction with the PK-guided dose adjustment for each cycle (5-FU<sub>LODPM</sub> Protocol™, Angers, France) is the key to avoiding 100% of deaths related to early-onset toxicities and 98% of severe early-onset toxicities (Grade 3 and 4).

**RESULTS:**

- **5-FU dose adjustment:** 6 patients received initial reduced dose of 5-FU (5 because of major DPD deficiency, 1 elderly).
- **CPT11 dose adjustment:** Mean dose at 3 months was 256±50mg/m² for 6/6 patients, 184±53mg/m² for 6/7 patients, 127±14mg/m² for 7/7 patients.
- **Toxicity analysis:** 5-FU-related → mainly HFS and mucositis; CPT11-related → neutropenia and diarrhea (see Table 1).

**CONCLUSIONS:**

5-FU tailored therapy: toxicity was mild, because of the pre-therapeutic screening (5-FU<sub>LODPM</sub>™) and 5-FU dose monitoring (5-FU<sub>LODPM</sub> Protocol™). Large individual dose increases (up to 4117 mg/m²), and a very large inter-individual dose range (722-4117 mg/m²) was necessary to reach targeted plasma concentration.

CPT11 tailored therapy: the current dose (180 mg/m²) is only correct for the 6/7 pts, whereas the 6/6 pts. are underdosed and the 7/7 pts. experience overexposure at that level. This study shows that neither dose reduction nor augmentation are pejorative for response rate and/or toxicity. Pre-therapeutic DPD and UGT1A1 enzyme analyses, combined with 5-FU PK-monitoring, offer each patient the correct dose of each molecule, with a fully manageable toxicity profile and a controlled doses optimization.