5,10-methylenetetrahydrofolic acid with 5-fluorouracil as first line treatment in metastatic colorectal cancer: phase II study results

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Background: 5-Fluorouracil (FU) plus Leucovorin (LV) has historically been the standard first line treatment of colorectal cancer. Although LV modestly enhances FU activity, it can increase systemic toxicity and also must be intracellularly converted in multiple steps to its active metabolite, 5,10-methylenetetrahydrofolate (CoFactor, CO). Unlike LV, CO directly modulates FU inhibition of thymidylate synthase without the need for metabolic conversion. Preclinical models show reduced hematologic toxicity of CO+FU with enhanced efficacy compared to FU+LV. We evaluated CO+FU chemotherapy in patients with previously untreated mCRC. **Methods:** Patients (pts) had performance status ECOG 0-2 and objectively measurable mCRC. Prior adjuvant therapy was allowed including FU+LV. Fifty pts were enrolled and treated with CO 60mg/m^2 and FU 450mg/m^2 (weekly IV bolus) for 6 weeks, followed by 14 day rest. Response was measured at 16 wks (WHO criteria). **Results:** As of June 2006, 50 pts received at least 1 dose of drug and are no longer on treatment. Patient demographics: median age = 65 (range 42-86), M/F = 60%/40%. Mean number of doses was 18.0 (range 2-41). Overall incidence of grade 3/4 AEs was 11 (22%). No grade 3/4 drug-related hematologic toxicity was observed. There was no significant effect on HCT, Bili, WBC, ALT, and AST during the course of the study. Objective response rate (CR + PR) based on independent blinded review was 35% (2 CR, 14 PR, 4 MR, 19 SD, 7 PD; 95% CI: 21.4-50.2) based on 46 pts evaluable for response. Median time to tumor progression was 162 days (95% CI: 105 -166). Twenty-eight pts are deceased and median survival was 459 days (95% CI: 335 -699). **Conclusions:** The results suggest that CO+FU is safe, well tolerated, and has activity in mCRC. In the optimum treatment strategy afforded by the availability of numerous drugs, the high level of activity and low toxicity of CO+FU suggests that this combination may be a good initial treatment in a sequential strategy of mCRC management, especially among pts who would benefit by minimizing initial toxicity.

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