5-FLUOROURACIL EXPOSURE PREDICTS DISEASE-FREE SURVIVAL IN ADJUVANT CHEMOTHERAPY FOR COLORECTAL CANCERS

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Background and Aim. 5-Fluorouracil (5-FU) is still the mainstay in adjuvant protocols for colorectal cancers (CRC). Several studies have investigated the disease free survival (DFS) improvement after fluoropyrimidine-based adjuvant chemotherapy, despite data concerning the possible role of 5-FU exposure on DFS are not yet available. The present study was aimed at evaluating possible correlations between pharmacokinetics of 5-FU and the first inactive metabolite 5-fluoro-5,6-dihydrouracil (5-FDHU) and DFS in CRC patients candidate to receive 5-FU-based adjuvant chemotherapy. **Patients and Methods.** From January 1997 to December 1999, 101 consecutive CRC patients, 66 men and 35 women (age [mean±standard deviation], 61.8±9.3 and 58.2±8.7 years, respectively), were enrolled. Planned treatment consisted of six cycles of L-leucovorin 100 mg/m^2 and 5-FU 370 mg/m^2 administered as iv boluses for 5 consecutive days every 4 weeks. Blood samples, withdrawn on day 1 of the first cycle, were analysed for 5-FU and 5-FDHU plasma levels by a validated UV-HPLC method. Individual plasma concentrations of drug and catabolite were fitted according to a 2-compartment open model and the area under the time/concentration curve (AUC) value was calculated. Pathological features of tumours (stage and histological grade) were recorded, as well as relevant clinical and laboratory information during the entire course of planned chemotherapy. Univariate and multivariate analyses were performed, and results were expressed as mean±standard deviation values. *P* values lower than 0.05 were considered significant. **Results**. In this study, 44 patients (31 males and 13 females) experienced disease recurrence, and in 86% of them the disease recurred within 3 years of study entry. Tumour staging and histological grade did not affect significantly DFS among patients, whereas age significantly differed in disease-free patients with respect to other subjects (58.9±9.1 vs 62.7±8.9 years, respectively). Noteworthy, 5-FU AUC and 5-FU/5-FDHU AUC ratio were significantly lower in patients who experienced a recurrence with respect to other subjects (9.28±4.05 and 7.46±2.87 h×mg/l, 0.96±0.57 and 0.76±0.35, respectively), demonstrating a significant association between 5-FU exposure and DFS. Multivariate analysis showed that 5-FU AUC values lower than 7.9 h×mg/l were a risk factor of disease relapse within the first 5 years. **Conclusions.** Although the large interpatient variability observed in the present study, analysis performed on pharmacokinetic data demonstrates for the first time that reduced 5-FU AUC values are significantly associated with decreased DFS in CRC patients.