CHRONOTHERAPY WITH 5-FLUOROURACIL (5-FU) AND FOLINIC ACID (FA) IN ADVANCED COLORECTAL CARCINOMA: RESULTS OF A CHRONOPHARMACOLOGIC PHASE I/II TRIAL.

S. Adler, S. Lang, I. Langenmayer, B. Eibl-Eibesfeldt°, W. Rump, B.Emmerich, and M. Hallek

Most attempts to improve the survival of patients with advanced colorectal cancer have been frustrating. 5-FU ist still the single most effective drug which induces tumor remissions in <20% of the cases. Its antineoplastic activity is enhanced by the concomitant application of FA. This combination, however, has considerable side effects. The circadian timing of antineoplastic drug application (= chronotherapy) is a rather new strategy of reducing cytotoxic side effects. Stimulated by observations of a higher efficacy and lower toxicity of 5-FU by an appropriate circadian timing, we conducted a chronopharmacologic phase I/II trial with 5-FU and FA in 8 patients with advanced colorectal cancer. Patients (pts) received 5-FU and FA at starting doses of 500 mg/m^2/d and 20 mg/m^2/d over 5 consecutive days per treatment course. Treatment courses were repeated after 28 days. Dose escalations of 250 mg/m^2/d 5-FU and 10 mg/m^2/d FA per course were performed in the absence of any toxicity ≥ WHO grade III. Using a portable, ambulatory drug delivery system allowing rectangular changes of the infusion rate (Chronomat, Fresenius, Germany), 75% of the daily doses of 5-FU and FA were given as constant i.v. infusion from midnight to 7h00, and the remaining 25% during the rest of the day.

Dose-limiting toxicity WHO grade III was observed at 5-FU and FA doses of 750 and 30 mg/m^2/d in 5 pts, and 1000 and 40 mg/m^2/d in 3 pts, respectively. Mucositis was the dose-limiting toxicity in 6 pts. A partial clinical remission was achieved in 1 pt, and a stabilization in 2 pts. In the remaining 5 pts, a disease progression occured despite treatment with maximally tolerated doses. The maximally tolerated doses were slightly higher than the average doses reported by conventional phase I/II trials with 5-FU and FA, but clearly lower than those recently reported in a chronotherapeutic trial in which a different, sinusoidal mode of drug application was used (Lévi, Cancer 70:893, 1992). Therefore, we feel justified to caution that the circadian modulation of a given treatment protocol such as 5-FU plus FA may not always allow the safe application of very high doses. Specific delivery systems may be needed in order to make chronotherapy with 5-FU and FA relevant for patients with colorectal carcinoma.

Medizinische Klinik, and °Chirurgische Klinik, Klinikum Innenstadt, Universität München, Germany