Cancer Chemother Pharmacol (1987) 20: 71–74

Cancer Chemotherapy and Pharmacology

Relationship between systemic 5-FU passage and response in colorectal cancer patients treated with intrahepatic chemotherapy

Gérard Milano, Moise Namer, Jean-Louis Boublil, Roger Khater, Marc Frenay, Antoine Thyss, Jacques Bourry, Claire Philip, Nicole Renée, and Jean-Noel Bruneton

Centre Antoine-Lacassagne, 36 Voie Romaine, F-06054 Nice Cedex, France

Summary. The study described herein was conducted to analyze the relationship between tumor exposure to 5-FU and clinical response. Six patients were placed on continuous 5-day intrahepatic 5-FU chemotherapy for colorectal cancer metastasized to the liver. The starting dose was 600–800 mg/m^2 per day; cycles were repeated at 4-week intervals. The 5-FU dose was increased by 250 mg/day at each cycle. All six patients received 3 or more cycles, for a total of 37 cycles. Response was evaluated after each cycle by ultrasonography or computed tomography (CT). Pharmacokinetic data revealed a high individual cycle-to-cycle variability for all six patients in the 5-FU area under the curve (AUC day 1 to day 5) corrected for the dose. These variations in drug biodisposition, reflecting hepatic 5-FU uptake, were significantly related to measurable modifications in the tumor mass in 71% of cycles. The correlation between the reduction in local drug exposure and tumor regrowth was better than that between the increase in local drug exposure and tumor reduction. These findings constitute an original illustration in humans of the experimental concept of the drug exposure/tumor response relationship for 5-FU.

Introduction

Although response rate (20%) of colorectal cancer to chemotherapy with 5-fluorouridine (5-FU) is far from satisfactory [6], 5-FU and other fluoropyrimidines remain the most effective drugs for this pathology [12]. Metastasis to the liver occurs with disease progresion, and intra-arterial hepatic (IAH) chemotherapy with 5-FU is increasingly being used in attempts to improve the response rate and survival for such patients [2, 17]. The principle behind this therapeutic approach is local overexposure of tumor tissues to the drug, with concomitant systemic reduction of circulating cytotoxic drug levels [5]. In a recent pharmacokinetic study on locoregional 5-FU chemotherapy for colorectal cancer, we reported high intra- and interindividual variations in the systemic passage of this antimetabolite [4]. It was thus felt that a retrospective analysis of the possible repercussions of individual variations in local drug exposure for tumor response would be worthwhile. A total of 37 cycles of IAH chemotherapy with increasing doses of 5-FU were thus analyzed; these were administered to six patients being treated for liver metastasis from colorectal primary tumors.

Offprint requests to: Gérard Milano

Materials and methods

Six patients (5 men, 1 woman; mean age 67 years, range 62–74) who had liver metastases from colorectal cancer and had not previously been treated with chemotherapy were entered in the study. Liver lesions were assessed monthly by ultrasound and every 2 months by CT scans. We did not observe any major differences in the results obtained with these two imaging techniques. The tumor mass was expressed as the mean of the products of the two longest perpendicular diameters of all measurable metastases. None of the six patients had any extrahepatic metastases.

Pretreatment biological parameters for all patients were as follows: bilirubin <1.5 mg/dl, WBC $>3000/\text{mm}^3$, platelets $>100000/\text{mm}^3$, ECOG performance status ≤ 2. Catheterization of the gastroduodenal artery was performed surgically using an implantable port (Port-a-Cath, Pharmacia, France). Angiography was performed prior to each cycle to verify the position of the catheter.

5-Fluorouracil (Roche, France) was administered continuously over a period of 5 days using an external infusion pump (Fresenius, France); the cycle was repeated every 4 weeks. The initial dose of 600–800 mg/m^2 per day was increased at each cycle by 250 mg/day or more, depending on clinical and hematological tolerance.

The hepatic tumor mass of each patient was evaluated by the same investigator (JNB) before the start of each cycle. The following blood tests were also performed: liver enzymes, bilirubin, CEA, WBC, RBC, hemoglobin and platelet count. Blood samples were obtained by venous puncture at 8 a. m. and 5 p. m. on every day of each cycle. This twice-a-day sampling procedure was selected with a view to patient comfort and on the basis of personal observations (unpublished data) showing that plasma levels of 5-FU were stable between morning and evening when constant-flow-rate pumps were used. Samples were collected in EDTA tubes and centrifuged immediately; the supernatant was stored at $-20°$ C until analyzed. 5-FU was quantified by a specific HPLC method [4] using 5-fluorocytosine as the internal standard.

The area under the curve (AUC) was calculated by the trapezoidal rule from 5 p. m. on day 1 to 5 p. m. on day 5. A total of 37 cycles were analyzed; patients received an average of 6 cycles (range 3–11). All patients were evaluable for hepatic tumoral response at the start of each cycle.

In order to analyze the relationship between individual variation in tumoral exposure to 5-FU and modifications in the tumor mass, the following parameters were defined:

$$Q_{AUC\,(n,\,n+1)} = \frac{AUC/dose\ (n)}{AUC/dose\ (n+1)}$$

$$Q_{V(n,\,n+1)} = \frac{V\ (n)}{V\ (n+1)}$$

Where AUC/dose (n) is the area under the curve for the systemic drug concentration from 5 p. m. on day 1 to 5 p. m. on day 5 of cycle n, corrected for the dose

and V (n) is the tumoral mass after administration of cycle n, evaluated 4 weeks after and just before the start of cycle n + 1

With due consideration for analytical inaccuracy in AUC determination (5%) and tumor mass evaluation (10%), a $Q_{AUC\,(n,\,n+1)}$ of 0.9 or less from cycle n to cycle n + 1 indicates a decrease in local exposure to 5-FU from cycle n to cycle n + 1 while a $Q_{AUC\,(n,\,n+1)}$ of 1.1 or more indicates an increase.

A $Q_{V\,(n,\,n+1)}$ of 0.80 or less is considered to reflect an objective increase in the hepatic tumoral mass from cycle n to cycle n + 1. A $Q_{V\,(n,\,n+1)}$ 1.20 or more is considered to reflect an objective decrease.

In theory, the correct individual associations are:

$Q_{AUC\,(n,\,n+1)} \leq 0.9$ and $Q_{V\,(n,\,n+1)} \leq 0.80$ = reduction in the local exposure to the drug from cycle n to cycle n + 1 and an increase in the hepatic tumor mass from cycle n to cycle n + 1

$Q_{AUC\,(n,\,n+1)} \geq 1.10$ and $Q_{V\,(n,\,n+1)} \geq 1.20$ = increase in the local exposure to the drug from cycle n to cycle n + 1 and a decrease in the hepatic tumor mass from cycle n to cycle n + 1

Associations were evaluated statistically using the null hypothesis test, with No = 0.5 (frequency of random association) according to a binomial law.

Results

Figure 1 allows comparison of the variations of individual 5-FU disposition and hepatic tumor mass for all patients and all cycles. In the majority of cases, evolution of the area under the curve corrected for the dose (AUC/dose) fluctuated during the course of treatment. Although the variability in systemic drug evolution appears to be independent of dose, the amplitude of variation is particularly marked following high 5-FU doses. The tumor mass is modified by treatment, and such modifications are globally similar to those observed for the AUC/dose. Figure 2 illustrates the association between an individual change in local exposure to the drug from one cycle to the next (Q_{AUC}) and the variation in tumor mass observed during this same period (Q_V).

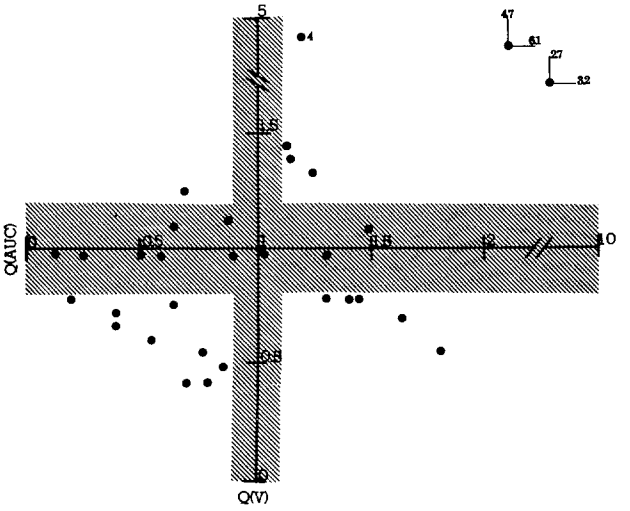

Fig. 2. Individual associations between variations in AUC/dose from cycle to cycle (Q_{AUC}) and evolution of tumor mass (Q_V). *Shaded area:* low-accuracy data (see *Materials and methods).*

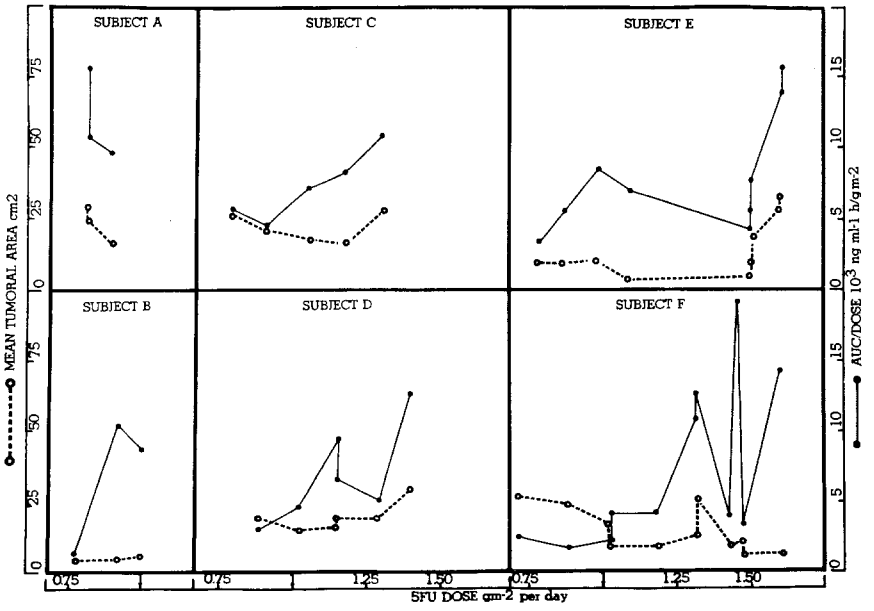

Fig. 1. Concomitant individual evolutions of AUC/dose and hepatic tumor mass for all patients and all cycles

Of the 31 modifications available for analysis only 21 could be interpreted, in view of the previously defined restrictions concerning accuracy in AUC and tumor mass measurement, and 15 (71%) of these 21 associations were correctly related ($P<0.05$). The figure obtained when all cycles were considered without this measurement restriction is similar: 21/31, i. e., 68%. The association was better between a reduction in local drug exposure ($Q_{AUC} \leq 0.9$) and an increase in hepatic metastasis ($Q_V \leq 0.8$) (9/10 cases, $P<0.01$) than in the opposite situation ($Q_{AUC} \geq 1.1$, $Q_V \geq 1.2$; not significant).

Discussion

During the pharmacoclinical follow-up of 37 cycles of IAH 5-FU chemotherapy with dose escalation, a considerable intra- and interindividual dose-dependent variability was observed in systemic passage of the drug (AUC). The variability of 5-FU pharmacokinetics has recently been reported in connection with high drug doses administered by i. v. perfusion [15]. Our findings show that the liver is largely responsible for this variability. Nevertheless, the actual cause of this relative instability in local drug extraction during treatment remains hard to explain. All six patients had implantable ports, and the drug was thus perfused under the same local delivery conditions for all cycles.

Like other authors [8], we have established [4] that IAH 5-FU infusions result in elevated extraction rates (>90%) that are saturated at high doses. The variability in hepatic drug extraction might thus be the result of a reversible saturation phenomenon. An individual modification in the hepatic arterial flow rate might also play a significant role in the degree of presystemic uptake of such a highly extracted drug as 5-FU [13].

It is also difficult to determine the respective roles of the normal liver parenchyma and the tumor tissue in global hepatic 5-FU extraction, but it is well known that the hepatic artery primarily supplies the tumor area in cases of liver metastasis [1]. Previous investigators have observed a positive correlation between 5-FU bioavailability and response in patients with metastatic colorectal cancer treated by i. v. infusion [10, 16]. We failed to find such a correlation for head and neck cancer patients treated with *cis*-platinum plus 5 days of 5-FU [18]. These previous studies, however, were not methodically satisfactory, which precluded significant conclusions: the nature of the tumor targets was not uniform, and neither were the treatment itself (5-FU + methyl CCNU (10)) and the form of 5-FU administration [16].

The present study is based on analysis of the individual modifications in drug uptake at each cycle as a function of the subsequent evolution of a measurable target. Systemic passage of 5-FU after IAH administration is assumed to be a representative parameter of presystemic hepatic uptake in view of the high hepatic extraction rates reported.

On an individual cycle-to-cycle basis, a significant, positive association was noted between a variation in the AUC, which indirectly reflects a change in local drug response, and a modification in hepatic tumor size measured 4 weeks later. Changes in the systemic disposition of the drug were thus correlated with variations in tumor mass. These findings constitute an original illustration in humans of the marked drug exposure/tumor response relationship for 5-FU previously established experimentally [9, 14]. However, the relationship was less satisfactory for increases in tissue exposure to the drug related to regression of hepatic metastases than for the opposite situation. One possible explanation for this might be a limited capacity of the intracellular systems, which obligatorily activate 5-FU into its cytotoxic forms [13]. The role of 5-FU anabolism must not be overestimated, however; differences in the cellular content of active forms of 5-FU (FdUMP) have not been shown experimentally to explain the variability in 5-FU sensitivity [11].

The fact that a reduction in local 5-FU delivery is followed in 90% of cases by measurable tumor regrowth is of particular interest. This observation has clinical implications, as the decision to reduce individual drug doses, at least for 5-FU given for IAH treatment, must be carefully weighed against the possibility of tumor 'escape'. Use of IAH chemotherapy is increasingly more common, even though no superiority over i. v. infusions has yet been proven in terms of survival benefit [3]. The various means utilized in attempts to increase tissue uptake of the drug have recently been reviewed [7]. Our findings reveal that determination of the pharmacokinetic behavior of 5-FU is justified as a complement to clinical trials for objective evaluation of various modalities in IAH treatment by 5-FU.

Acknowledgement: To Nancy Rameau for assistance with translation.

References

1. Ackerman NB, Lien WM, Kondi ES, Silverman NA (1969) The blood supply of experimental liver metastases. The distribution of hepatic artery and portal vein blood to "small" and "large" tumors Surgery 66: 1067–1072
2. Barone RM, Byfield JE, Goldfarb PB, Frankel S, Ginn G, Greer S (1982) Intra-arterial chemotherapy using an implantable infusion pump and liver irradiation for the treatment of hepatic metastases. Cancer 50: 850–862
3. Bedikian AY, Chen TT, Malahy MA, Patt YZ, Bodey GP (1984) Prognostic factors influencing survival of patients with advanced colorectal cancer: hepatic-artery infusion versus systemic intravenous chemotherapy for liver metastases. J Clin Oncol 2: 174–180
4. Boublil JL, Milano G, Khater R, Bourry J, Thyss A, Bruneton JN, Renee N, Philip C, Namer M (1985) Continuous 5-day regional chemotherapy by 5-fluorouracil in colon carcinoma: Pharmacokinetics evaluation. Br J Cancer 52: 15–20
5. Chen GHS, Gross JF (1980) Intra-arterial infusion of anticancer drugs: theoretic aspects of drug delivery and review of responses. Cancer Treat Rep 64: 31–40
6. Davis HL (1982) Chemotherapy of large bowel cancer. Cancer 50: 2638–2646
7. Ensminger DW, Gyves JW (1983) Regional chemotherapy of neoplastic diseases. Pharmacol Ther 21: 277–293
8. Ensminger DW, Stetson P, Gyves JW, Walker S, Janis M, Zlotecki R, Meyer M, Brady T, Niederhuber J (1983) Dependence of hepatic arterial fluorouracil pharmacokinetics on dose rate and duration of infusion. Proc ASCO 2: C-98 (abstract)
9. Frei E III, Garnick MB, Ensminger WD, Israel M, Steele GD, Kaplan WD, Come SE (1981) Biochemical pharmacology in medical oncology. Cancer Treat Rep 65 [Suppl 3]: 21–26
10. Hillcoat BL, McCulloch PB, Figueredo AT, Ehsan MH, Rosenfeld JM (1978) Clinical response and plasma levels of 5-fluorouracil in patients with colonic cancer treated by drug infusion. Br J Cancer 38: 719–724

11. Houghton JA, Maroda SJ, Phillips JO, Houghton PJ (1981) Biochemical determinants of responsiveness to 5-fluorouracil and its derivatives in xenografts of human colorectal adenocarcinoma in mice. Cancer Res 41: 144–149
12. Metzger UF, Ghosh BC, Kisner DL (1985) Adjuvant treatment of colorectal cancer. Current status and concepts. Cancer Chemother Pharmacol 14: 1–8
13. Rowland M, Tozer TN (1980) Hepatic clearance and elimination. In: Rowland M, Tozer TN (eds) Clinical pharmacokinetics. Concepts and applications. Lea and Febiger, Philadelphia pp 65–76
14. Schabel FM, Griswold DP, Corbett TH, Laster WR (1983) Increasing therapeutic response rates to anticancer drugs by applying the basic principles of pharmacology. Pharmacol Ther 20: 283–305
15. Schwartz PM, Turek PJ, Hyde CM, Cadman EC, Handschumacher RE (1985) Altered plasma kinetics of 5-FU at high dosage in rat and man. Cancer Treat Rep 69: 133–136
16. Seitz JF, Cano JP, Rigault JP, Aubert C, Carcassonne Y (1983) Chimiothérapie des cancers digestifs étendus par le 5-fluorouracile: relations entre la réponse clinique et la clairance plasmatique du médicament. Gastroenterol Clin Biol 7: 374–380
17. Stagg RJ, Lewis BJ, Friedman MA, Knoffo RJ, Hohn DC (1984) Hepatic arterial chemotherapy for colorectal cancer metastatic to the liver. Ann Intern Med 100: 736–743
18. Thyss A, Milano G, Renée N, Vallicioni J, Schneider M, Demard F (1986) Clinical pharmacokinetic study of 5-FU in continuous 5-day infusions for head and neck cancers. Cancer Chemother Pharmacol 16: 64–66

Received October 14, 1985/Accepted March 6, 1987