J. Pharm. Pharmacol. 1994, 46: 685–689
Received March 8, 1993
Accepted January 17, 1994

Pharmacokinetic Characteristics of 5-Fluorouracil and Mitomycin C in Intraperitoneal Chemotherapy

TAKAFUMI KUZUYA, MASAJI YAMAUCHI*, AKIHIRO ITO*, MASAYA HASEGAWA, TAKAAKI HASEGAWA AND TOSHITAKA NABESHIMA

*Department of Hospital Pharmacy and *Second Department of Surgery, Nagoya University School of Medicine, Nagoya, Japan*

Abstract—Eight patients with malignancies confined to the peritoneal space participated in this study. Five hundred milligrams 5-fluorouracil or 10 mg mitomycin C was diluted in 1 L saline. The mixed solution was injected intraperitoneally through the semi-permanent peritoneal catheter. Blood and peritoneal fluid were collected after injection. 5-Fluorouracil concentrations in the peritoneal fluid were 1000 times those in serum, while mitomycin C concentrations were 100 times those in serum. Areas under the concentration vs time curve (AUC) were calculated by the trapezoidal method with extrapolation to infinity. The ratio of peritoneal fluid AUC to serum AUC was about 1400 for 5-fluorouracil and 80 for mitomycin C. Patterns for the absorption and elimination from systemic circulation were similar for both compounds. Drug concentrations in the peritoneal fluid and serum were analysed according to the compartment model. The half-life in the peritoneal fluid ($t_{\frac{1}{2}p}$) and the rate constant from the peritoneal fluid to the systemic circulation (k_a) were nearly equal for both 5-fluorouracil and mitomycin C ($t_{\frac{1}{2}p}$, 1·0 h for 5-fluorouracil and 1·3 h for mitomycin C; k_a 0·71 h^{-1} for 5-fluorouracil and 0·68 h^{-1} for mitomycin C), although the apparent volume of distribution (Vd_s/F) and clearance in the peritoneal cavity (CL_p) for mitomycin C (78 L m^{-2} and 1.8 L h^{-1} m^{-2}) were about twice the values for 5-fluorouracil (149 L m^{-2} and 0·8 L h^{-1} m^{-2}).

Many patients with gastrointestinal and ovarian tumours develop extensive peritoneal and serosal metastases. Intra-abdominal tumours are often the primary cause of liver metastases, spreading through portal venous drainage (Wood et al 1976), and ascites leading to anorexia and nausea. This area is also one of the most difficult to treat with chemotherapy. A variety of approaches, including radioisotopes, systemic chemotherapy and locally directed chemotherapy, has been attempted to treat intra-abdominal tumours. Within the last decade many oncologists have been conducting locally directed intraperitoneal administration through a semi-permanent peritoneal catheter using various antitumour drugs and treatment schedules (Myers & Collins 1983; Brenner 1986; McClay & Howell 1990). Chemotherapy treatment by the intraperitoneal route delivers high local concentrations to the peritoneal cavity while producing low concentrations in the systemic circulation. With this method of chemotherapy, various adverse effects, such as nausea, vomiting, mucosites, bone marrow suppression and renal impairment can be eliminated or greatly reduced. In addition, repetitive administration can be conducted easily in outpatients.

Recent reports have discussed the relationship between drug concentration or exposure time and the cell-killing effect for both cell cycle phase-specific agents and phase-nonspecific agents (Ozawa et al 1988). We undertook this study by fitting the compartment model to locally directed intraperitoneal chemotherapy using 5-fluorouracil and mitomycin C. Pharmacokinetic parameters were analysed by measuring drug concentrations in both the peritoneal fluid and serum, and by estimating the pharmacokinetic properties for each drug.

Correspondence: T. Hasegawa, Department of Hospital Pharmacy, Nagoya University School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466, Japan.

Materials and Methods

Materials

5-Fluorouracil and mitomycin C for clinical use were purchased from Kyowa Hakko Kogyo Co. (Tokyo, Japan). All standard reagents for analysis were donated by the same company. Other chemicals were obtained from standard chemical sources and were of analytical reagent grade.

Patients

Eight Japanese patients hospitalized at Nagoya University Hospital had been diagnosed histologically to be suffering from gastrointestinal cancer. The characteristics and histology of the patients are listed in Table 1. Informed consent was obtained from each patient after a full explanation of the procedure of the study.

Surgery and chemotherapy

Surgery was undertaken to remove any tumours. If the malignancy was confined to the peritoneal space and was considered a measurable or assessable disease by histology, then a semi-permanent peritoneal catheter was inserted. The standard Tenckhoff flexible Silastic peritoneal dialysis catheter was inserted into the Douglas pouch and was passed subcutaneously to a stainless-steel port as described by McClay & Howell (1990).

Chemotherapy was started one week after surgery and was conducted once a week. Five hundred milligrams 5-fluorouracil, 10 mg mitomycin C or 50 mg cisplatin were diluted in 1 L saline; the present study did not deal with the

Table 1. Patient characteristics.

Patient no.	Age (yr)	Sex	Body wt (kg)	Primary tumour	Stage at laparotomy	Operation	Treatment	Response
1	52	M	64	Stomach	IV	Partial gastrectomy	5-Fluorouracil, mitomycin C	Complete
2	37	F	41	Stomach	III	Total gastrectomy	5-Fluorouracil, mitomycin C	Stable
3	58	F	47·5	Colon	IV	Colectomy	5-Fluorouracil	Stable
4	48	M	53	Stomach	III	Total gastrectomy	5-Fluorouracil	Stable
5	57	F	34	Stomach	IV	Colectomy	5-Fluorouracil	Partial
6	50	M	50	Stomach	IV	Colectomy	5-Fluorouracil, mitomycin C	Progressive disease
7	52	M	57	Stomach	IV	Partial gastrectomy	Mitomycin C	Progressive disease
8	63	M	40	Stomach	III	Total gastrectomy	Mitomycin C	Stable

cisplatin data. The mixed solution was then injected intraperitoneally. The method for selecting the drugs in this study was according to the methylthiazol tetrazolium bromide assay that has been widely used to evaluate the sensitivity of cancer cells to agent (Wilson et al 1990; Yamauchi et al 1991). Peritoneal fluid samples were collected at 0·5, 1, 3, 6, 12, and 24 h after the injection. Blood samples were also taken at the same times as above with four of six patients for 5-fluorouracil and three of four patients for mitomycin C. Serum was separated immediately after collection. Both serum and peritoneal samples were stored at −30°C until analysis.

Drug analysis

Concentrations of the two drugs in the peritoneal fluid and serum samples were determined by high-performance liquid chromatography (HPLC). HPLC analysis was carried out using a Shimadzu LC-6A system (Shimadzu Co., Kyoto, Japan) with a Cosmosil ODS column (4·6 i.d. × 25 cm; Nacalai Tesque, Kyoto, Japan). 5-Fluorouracil concentration was assayed according to the method of Buckpitt & Boyd (1980) with minor changes. Briefly, 250 μL distilled water containing an internal standard (0·5 μg mL^{-1} 5-chlorouracil), 100 μL 0·5 M phosphate buffer (pH 8·0) and 6 mL ethyl acetate were added to 500 μL sample and then mixed vigorously. The resultant organic layer was separated and evaporated with N_2 gas at 50°C. The residue was reconstituted with the mobile phase (0·01 M KH_2PO_4, pH 4·0) and injected onto the HPLC. Standard curves for determination of 5-fluorouracil were constructed by plotting the ratio of the peak heights for drug and internal standard against the known drug concentrations in standard samples.

The concentration of mitomycin C was determined by a modification of the method previously reported (Kono et al 1979). One millilitre sample was extracted with 8 mL ethyl acetate. Seven millilitres organic layer was separated and evaporated as described above, and the mobile phase (methanol–water, 35:65) was added to the residue and injected onto the HPLC. Standard curves were obtained by plotting the peak heights against the amounts of mitomycin C injected. The limits of quantitation were 5 ng mL^{-1} for 5-fluorouracil and 10 ng mL^{-1} for mitomycin C, respectively. The intra-day and inter-day coefficients of variation for both drugs were less than 5%.

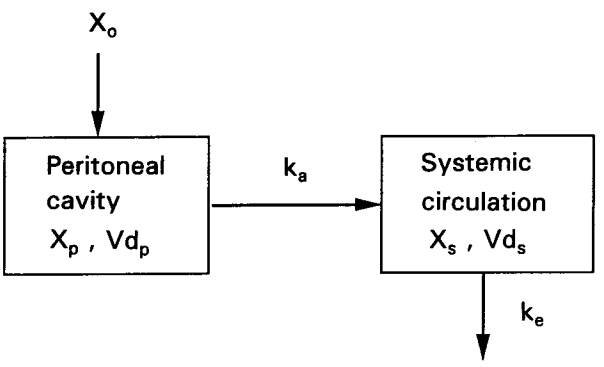

FIG. 1. Compartment model for peritoneal administration.

Pharmacokinetic calculations

Data were analysed according to the compartment model as illustrated in Fig. 1. The drug was easily distributed throughout the peritoneal cavity following a rapid intraperitoneal injection after which it entered the systemic circulation and suffered a first-pass effect. The drug was then metabolized, or excreted into the urine from the systemic circulation.

The rate for drug loss from intraperitoneal administration was calculated using equation 1. The drug, which entered into the systemic circulation at an apparent first-order rate, was likewise eliminated through a first-order process according to equation 2. The results of these two equations could subsequently be applied for equations 3 and 4.

$$\frac{dX_p}{dt} = -k_a X_p \quad (1)$$

$$\frac{dX_s}{dt} = k_a X_p - k_e X_s \quad (2)$$

$$C_p = \frac{X_0}{Vd_p} e^{-k_a t} \quad (3)$$

$$C_s = \frac{F k_a X_0}{Vd_s(k_e - k_a)} (e^{-k\,at} - e^{-k_e t}) \quad (4)$$

where F is the fraction of the administered dose (X_0) that is absorbed following peritoneal administration, k_a is the apparent first-order absorption rate constant from the peritoneal cavity to the systemic circulation, k_e is the apparent first-order elimination rate constant from the

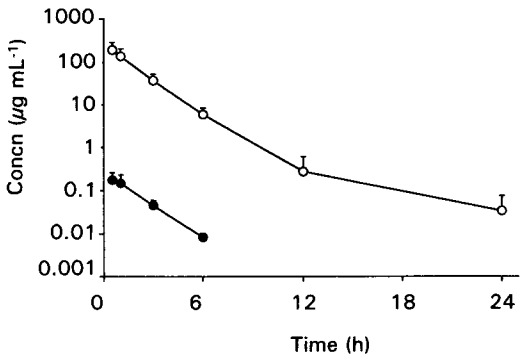

FIG. 2. Mean semilogarithmic plots of intraperitoneal (○) and serum (●) concentrations for 5-fluorouracil vs time after an intraperitoneal dose of 500 mg to six and four patients, respectively.

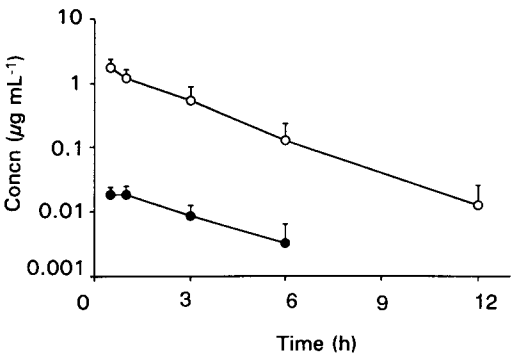

FIG. 3. Mean semilogarithmic plots of intraperitoneal (○) and serum (●) concentrations of mitomycin C vs time after an intraperitoneal dose of 10 mg to four and three patients, respectively.

systemic circulation, X_p and X_s are the amount of drug in the peritoneal cavity and in the systemic circulation, respectively, X_0 is the amount of injection, Vd_p and Vd_s are the apparent volume of distribution in the peritoneal cavity and in the systemic circulation, respectively, and t is time.

Vd_p and the elimination half-life for the drug in the peritoneal cavity ($t_{\frac{1}{2}p}$) were calculated based on the peritoneal drug concentration vs time curve using the nonlinear least-squares method (Yamaoka et al 1981). The parameters (k_a, k_e, Vd_s/F) represent the computer fitting curves generated by simultaneously solving the two differential equations (3,4). The elimination half-life for the drug in the systemic circulation was calculated from $t_{\frac{1}{2}s} = 0{\cdot}693/k_e$. Areas under the concentration vs time curves in the peritoneal fluid (AUC_p) and serum (AUC_s) were calculated by the trapezoidal method with extrapolation to infinity. Peritoneal clearance (CL_p) and systemic clearance (CL_s) were calculated as $CL_p = Dose/AUC_p$ and $CL_s = Dose\ F/AUC_s$, respectively.

Statistical analysis

Statistical analysis of the differences were performed by an unpaired *t*-test. All parameters were considered significant at $P < 0{\cdot}05$.

Results

The mean semilogarithmic peritoneal and serum concentration vs time curves for 5-fluorouracil and mitomycin C are shown in Figs 2 and 3, respectively. In the peritoneal fluid both drug-concentration curves were characterized by a mono-exponential decline which can be described as apparent first-order elimination. 5-Fluorouracil was rapidly absorbed from the peritoneal cavity and rapidly disappeared from the systemic circulation. Its concentration in the intraperitoneal cavity at any given time was more than 1000 times that in serum, while for mitomycin C the factor was 100 times. Patterns observed in the absorption and elimination were similar for both drugs.

The pharmacokinetic parameters in the peritoneal cavity and serum are summarized in Tables 2 and 3. The half-life for 5-fluorouracil in the peritoneal cavity was 1·04 h, which correlated well with data from Arbuck et al (1986) (0·97–1·13 h). The half-life for 5-fluorouracil in the systemic circulation ($t_{\frac{1}{2}s}$) was approximately 6 min. The mean peritoneal AUC (AUC_p) for 5-fluorouracil was approximately 1400 times greater than that in serum (AUC_s).

The half-lives for mitomycin C in the peritoneal cavity and in the systemic circulation were 1·33 h and 20 min, respectively. The AUC ratio of peritoneal fluid to serum (AUC_p/AUC_s) was about 80 for mitomycin C.

The pharmacokinetic parameters, $t_{\frac{1}{2}p}$ and k_a, were not statistically significantly different between the two drugs. However, Vd_p, CL_p, k_e, CL_s/F and Vd_s/F were significantly different ($P < 0{\cdot}05$), and CL_p for mitomycin C was about twice that for 5-fluorouracil.

Discussion

A number of studies have suggested that AUC might be the best pharmacokinetic parameter for predicting the response to cell cycle phase-specific and phase-nonspecific agents (Levin 1986). Targeted drug treatment via intraperitoneal injections enhances the effects of the drug as shown by the ratio of AUC_p to AUC_s, whereby a greater value of the ratio indicates the efficacy of such intraperitoneal treatment. One important factor affecting this ratio, however, is the per-

Table 2. Pharmacokinetic parameters in the peritoneal cavity after intraperitoneal treatment with 500 mg 5-fluorouracil and 10 mg mitomycin C.

Drug	$t_{\frac{1}{2}p}$ (h)	Vd_p ($L\,m^{-2}$)	CL_p ($L\,h^{-1}\,m^{-2}$)	AUC_p ($mg\,h\,L^{-1}$)
5-Fluorouracil	1·04 ± 0·36	1·52 ± 1·05	0·83 ± 0·32	475 ± 215
Mitomycin C	1·33 ± 0·61	3·12 ± 1·20	1·77 ± 1·26	4·87 ± 2·06

Each value represents mean ±s.d. (n = 6 for 5-fluorouracil and n = 4 for mitomycin C).

Table 3. Pharmacokinetic parameters in the serum and peritoneal cavity after intraperitoneal treatment with 500 mg 5-fluorouracil and 10 mg mitomycin C.

Drug	k_e (h^{-1})	k_a (h^{-1})*	CL_s/F ($L\,h^{-1}\,m^{-2}$)	AUC_s ($\mu g\,h\,L^{-1}$)	Vd_s/F ($L\,m^{-2}$)
5-Fluorouracil	6·94 ± 2·26	0·71 ± 0·26	940 ± 281	346 ± 154	149 ± 34
Mitomycin C	2·08 ± 1·29	0·68 ± 0·31	118 ± 34	59 ± 16	78 ± 60

Each value represents mean ± s.d. (n = 4 for 5-fluorouracil and n = 3 for mitomycin C). *No significant difference was noted between 5-fluorouracil and mitomycin C ($P > 0·5$).

meability of the peritoneal membranes. Drug absorption from the peritoneal membrane into the systemic circulation is primarily due to a passive diffusion mechanism (Kraft et al 1968), and depends on a number of factors including mol. wt, lipid solubility, ionization at the physiological pH for drugs, and in the disease states for patients (Torres et al 1978). Dedrick et al (1978) have reported an inverse relation between intraperitoneal clearance and mol. wt. Animal studies have also shown that the permeability of the peritoneal membrane decreases as mol. wt increases (Lukas et al 1971). The results from this study did not support such findings, showing that the mol. wt of a drug is a major determinant in the penetration of that drug since mol. wts for 5-fluorouracil and mitomycin C are 130·08 and 334·33, respectively, although the penetration of the latter was greater than that of the former based on the results of the AUC_p/AUC_s ratios.

This ratio represents yet another important factor: drugs administered intraperitoneally are principally distributed via portal venous drainage, although some of the drug is absorbed into the lymphatics (Lukas et al 1971). The primary characteristics of drugs with a high hepatic extraction ratio are that when administered intraperitoneally, first-pass metabolism is significant and the amount of drug reaching the systemic circulation may be markedly low when compared with the dosage administered. Thus, these first-pass effects, as well as the product of the volume of distribution and elimination rate constant, represented as systemic clearance ($k_e \cdot Vd_s$), can influence the values of AUC_s.

The ratio of AUC values for intravenous injection and other routes of administration is commonly used for calculating F. Finch et al (1979) reported the mean AUC of 5-fluorouracil as $8·45\,mg\,h\,L^{-1}$ after an intravenous administration of 500 mg. When the F value in the present study was calculated based on the AUC value from that study, the obtained F value was 0·041. This method of calculation is a non-compartment method based on the statistical moment theory. Another method which can be used to obtain the F value is from Vd_s/F, which depends on the compartmental model. The volume of distribution for 5-fluorouracil in the systemic circulation at the same dose as that used in this study has been reported to be 12·6 L (Fujita 1985). When calculated from these results, the resulting F value was 0·057 (mean area of body surface (m^2) = 1·481), a figure which is nearly equal to the value obtained by the non-compartmental model described above. These findings indicate that the compartmental model used in this study is an adequate model and that only 4–6% of the 5-fluorouracil dose is absorbed from the peritoneal cavity into the systemic circulation.

Speyer et al (1981) have also reported that the mean hepatic extraction ratio of 5-fluorouracil ranges from 0·71 to 0·74. Assuming that the disappearance of drug from the peritoneal cavity after an intraperitoneal injection depends only on the hepatic metabolism, the extract from the peritoneal cavity may be merely 30% less than the dose. From the results of their study coupled with the present findings (F = 0·041) using non-compartmental methods, it may be said that less than 86% of the administered dose is lost from the peritoneal cavity in the absence of distribution to the systemic circulation, probably due to factors such as peritoneal metabolism, binding to proteins and tissues in the peritoneal cavity, and through the lymphatics. Further studies, however, are required in this respect.

F values for mitomycin C as calculated from the AUC ratio (Fujita 1985) and Vd_s/F (Verweij et al 1986) in the same manner as described above were 0·213 and 0·245, respectively. The F value for mitomycin C was five times that for 5-fluorouracil. In addition, the systemic clearance of 5-fluorouracil has been reported to be about twice that of mitomycin C (0·947 vs $0·597\,L\,h^{-1}$) (Fujita 1985; Goldberg et al 1988). These discrepancies can be explained by observing the differences in the AUC ratio between the drugs.

Several investigators have reported the AUC ratio of 5-fluorouracil for peritoneal fluid to serum with values of 85–1150 (Schilsky et al 1990), 124–461 (Arbuck et al 1986) or 318 (Speyer et al 1981). These values are all lower than the value (1400) obtained in our study in spite of the same dose being used. We consider that the discrepancy is due to the variations in the volume of dialysate solution for administration, 1 L in our study, 2 L in the others. Furthermore, if the transportation of the dialysate solution from the peritoneal cavity to the systemic circulation is faster than the drug transportation, the expected values for drug concentration in the peritoneal fluid may be overestimated as time passes. When transportation of the dialysate solution was negligible, the semilogarithmic plots for the peritoneal fluid vs time curve would become more linear: concentrations for 5-fluorouracil and mitomycin C in the peritoneal cavity at 24 and 12 h, respectively, were slightly elevated. Although the exact absorption rate for the dialysate solution is unknown, it might be influenced by concentrations of various other substances or by osmotic pressure. It is unlikely that the volume of dialysate solution has an effect on the decline of the 5-fluorouracil concentration in the peritoneal cavity, since the half-life in the peritoneal cavity, using 1 L of dialysate solution, was in good agreement with the data using 2 L of solution reported by Arbuck et al (1986).

5-Fluorouracil and mitomycin C are active antitumour drugs used to treat solid tumours in various organs. The response of tumour cells to drugs increases as the concentration and duration of the particular drug increases. Various side-effects induced by clinical use of systemic chemotherapy, however, are limiting factors when adjusting the dosage. The findings from this study suggest that intraperitoneal administrations directly into the cavity containing tumour cells is beneficial in reducing various systemic side-effects.

References

Arbuck, S. G., Trave, F., Douglass, H. O., Nava, H., Zakrzewski, S., Rustum, Y. M. (1986) Phase I and pharmacologic studies of intraperitoneal leucovorin and 5-fluorouracil in patients with advanced cancer. J. Clin. Oncol. 4: 1510–1517

Brenner, D. E. (1986) Intraperitoneal chemotherapy: a review. J. Clin. Oncol. 4: 1135–1147

Buckpitt, A. R., Boyd, M. R. (1980) A sensitive method for determination of 5-fluorouracil and 5-fluoro-2-deoxyuridine in human plasma by high-pressure liquid chromatography. Anal. Biochem. 106: 432–437

Dedrick, R. L., Myers, C. E., Bungay, P. M., Devita, V. T. (1978) Pharmacokinetic rationale for peritoneal drug administration in the treatment of ovarian cancer. Cancer Treat. Rep. 62: 1–11

Finch, R. E., Bending, M. R., Lant, A. F. (1979) Plasma levels of 5-fluorouracil after oral and intravenous administration in cancer patients. Br. J. Clin. Pharmacol. 7: 613–617

Fujita, H. (1985) Pharmacokinetics of mitomycin C and 7-*N*-(*p*-hydroxyphenyl)-mitomycin C (KW-2083). In: Ishigami, J. (ed.) Recent Advances in Chemotherapy. University of Tokyo Press, Tokyo, pp 100–102

Goldberg, J. A., Kerr, D. J., Willmott, N., McKillop, J. H., McArdle, C. S. (1988) Pharmacokinetics and pharmacodynamics of locoregional 5-fluorouracil (5-FU) in advanced colorectal liver metastases. Br. J. Cancer 57: 186–189

Kono, A., Hara, Y., Eguchi, S., Tanaka, M. (1979) Determination of mitomycin C in biomedical specimens by high-performance liquid chromatography. J. Chromatogr. 164: 404–406

Kraft, A. R., Tompkins, R. K., Jesseph, J. E. (1968) Peritoneal electrolyte absorption: analysis of portal, systemic venous and lymphatic transport. Surgery 64: 148–153

Levin, V. A. (1986) Clinical anticancer pharmacology: some pharmacokinetic considerations. Cancer Treat. Rev. 13: 61–76

Lukas, G., Brindle, S. D., Greengard, P. (1971) The route of absorption of intraperitoneally administered compounds. J. Pharmacol. Exp. Ther. 178: 562–566

McClay, E. F., Howell, S. B. (1990) A review: intraperitoneal cisplatin in the management of patients with ovarian cancer. Gynecol. Oncol. 36: 1–6

Myers, C. E., Collins, J. M. (1983) Pharmacology of intraperitoneal chemotherapy. Cancer Invest. 1: 395–407

Ozawa, S., Sugiyama, Y., Mitsuhashi, Y., Kobayashi, T., Inaba, M. (1988) Cell killing action of cell cycle phase-non-specific antitumor agents is dependent on concentration-time product. Cancer Chemother. Pharmacol. 21: 185–190

Schilsky, R. L., Choi, K. E., Grayhack, J., Grimmer, D., Guarnieri, C., Fullem, L. (1990) Phase I clinical and pharmacologic study of intraperitoneal cisplatin and fluorouracil in patients with advanced intraabdominal cancer. J. Clin. Oncol. 8: 2054–2061

Speyer, J. L., Sugarbaker, P. H., Collins, J. M., Dedrick, R. L., Klecker, R. W., Myers, C. E. (1981) Portal level and hepatic clearance of 5-fluorouracil after intraperitoneal administration in humans. Cancer Res. 41: 1916–1922

Torres, I. J., Litterot, C. L., Guarino, A. M. (1978) Transport of model compounds across the peritoneal membrane in the rat. Pharmacology 17: 330–340

Verweij, J., Stuurman, M., Vries, J., Pinedo, H. M. (1986) The difference in pharmacokinetics of mitomycin C, given either as a single agent or as a part of combination chemotherapy. J. Cancer Res. Clin. Oncol. 112: 283–284

Wilson, J. K., Sargent, J. M., Elgie, A. W., Hill, J. G., Taylor, C. G. (1990) A feasibility study of the MTT assay for chemosensitivity testing in ovarian malignancy. Br. J. Cancer 62: 189–194

Wood, C. B., Gillis, C. R., Blumgart, L. H. (1976) A retrospective study of the natural history of patients with liver metastases from colorectal cancer. Clin. Oncol. 2: 285–288

Yamaoka, K., Tanigawara, Y., Nakagawa, T., Uno, T. (1981) A pharmacokinetic analysis program (MULTI) for microcomputer. J. Pharmacobiodyn. 4: 879–885

Yamauchi, M., Satta, T., Ito, A., Kondo, T., Takagi, H. (1991) A feasibility study of the SDI test for the evaluation of gastrointestinal cancer sensitivity to anticancer drugs. J. Sur. Oncol. 47: 253–260