Eur J Cancer Clin Oncol, Vol. 24, No. 2, pp. 175–180, 1988.
Printed in Great Britain

0277-5379/88$3.00+0.00

The Pharmacokinetic Plasma Profile of Mitomycin C, Measured After Sequential Intermittent Intravenous Administration*

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Abstract—*The pharmacokinetic plasma profile of mitomycin C (MMC) was studied during sequential courses in man. MMC was given repeatedly as i.v. bolus injections at fixed dose levels to the same patient either as a single agent or as part of different combination chemotherapy regimens. Large interindividual variations between the various pharmacokinetic parameters were observed. Statistical analysis showed no significant differences between average pharmacokinetic parameters when comparing the first and the second MMC injection, except for the total body clearance (Cl_{tot}). The Cl_{tot} was higher for the second injection when compared to the first injection in a group of patients who received MMC as a single agent (10 patients). For a group of patients receiving MMC as part of a combination therapy the average values of Cl_{tot} of the first when compared to the second injection were not statistically different (nine patients). This observation could not be correlated with clinical observations on toxicities.*

INTRODUCTION

MITOMYCIN C (MMC) is a frequently used antineoplastic agent in the treatment of several malignancies (for recent reviews see [1]). However, its widespread use is often limited by the frequent occurrence of, sometimes severe, toxicities during repeated injections of MMC. Several studies have been reported now on the pharmacokinetic behaviour of MMC [2–7]. In previous studies, a microbiologic assay was used for the determination of MMC in plasma and urine [2]. Because of the insensitivity and lack of selectivity of the latter method, especially in detecting MMC in the presence of other cytostatic agents, a high performance liquid chromatographic (HPLC) method was developed with a detection limit as low as 1 ng/ml [8]. The pharmacokinetic profile of MMC could best be described with a linear two-compartment model and the drug showed a non-dose dependent linear behaviour [3, 4]. Metabolism in the liver is supposed to be the major mechanism of elimination of MMC from the plasma [9]. No relation between pharmacokinetic data and toxicity has been established. The most significant and frequent toxicity of MMC in man is delayed myelosuppression, which appears to be directly related to the schedule and the total dose [10].

Other reported side-effects include usually mild and infrequent anorexia, nausea and vomiting, and diarrhoea. Alopecia, stomatitis and rashes occur infrequently. More serious and sometimes lethal side-effects have recently been reported to be pulmonary fibrosis, haemolytic uraemic syndrome and cardiac failure [11–17]. No data are available on the possible changes in the pharmacokinetics of MMC, induced by repeated intermittent administration and the occurrence of myelosuppression. The aim of the present study was to investigate whether intrapatient variations occur in the pharmacokinetics of MMC, when the drug is repeatedly given as i.v. bolus injections, at fixed doses and whether these might be related to the occurrence and extent of cumulative toxicities.

MATERIALS AND METHODS

Mitomycin C was obtained from Kyowa Hakko Kogyo Co. (Tokyo, Japan). All chemicals mentioned were of analytical reagent grade. Nineteen patients were included in this study, of which 10 received MMC as a single agent (group 1) at a dose range of 9–15 mg/m^2, while nine patients were treated with MMC at dose ranges of 5–10 mg/

Accepted 6 August 1987.
*This study was supported by the Netherlands Cancer Foundation (grant No. KWF THT 84-1) and by Kyowa Hakko Kogyo Co. (Tokyo, Japan).
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m^2 as part of different combination chemotherapy regimens (group 2). In multiple drug administration, MMC was the last drug administered. MMC was administered as an i.v. bolus injection (injection time 1–3 min at 6-week intervals). At least two pharmacokinetic curves were obtained from each patient. From seven patients at least three curves were available. Before treatment all patients were studied for complete blood counts, renal function, liver function and urinalysis. Blood samples were collected from the arm, opposite to the injection site through a cannula inserted into a vein, prior to MMC infusion, at 0, 2, 4, 10, 20, 30, 60, 120, 180, 240 and 300 min (or as close as possible) after injection in heparinized tubes.

Samples were ice-cooled. After centrifuging the plasma was separated and stored at −25°C. Urine was collected every hour for 3 h and stored at −25°C. Analysis of plasma was performed within 3 weeks, whereas urine was analysed within 2 weeks.

HPLC method

For analysis we used the assay described by Den Hartigh *et al.* [8]. Plasma and urine were extracted by liquid–liquid extraction (chloroform/isopropyl alcohol, 1:1, w/w). One millilitre of extraction solvent was added to 100 µl plasma. The chromatographic system consisted of a µBondapack C18 RP column, a Waters model 440 dual wavelength detector and a Waters Wisp 710 automatic injector. A methanol/0.01 M phosphate buffer (pH = 6.0, 3:7, w/w) was used as the eluent. Detection was performed at 365 nm, with Porfiromycin as internal standard (concentration 600 ng/ml). The limit of quantitation was 1 ng per ml plasma, collecting 1 ml samples. The recovery from plasma was ≥80%, measured over a concentration range of 5–2000 ng/ml. The precision of the method was ≤5%.

Pharmacokinetic calculations

For pharmacokinetic data analysis the same methods have been used as those reported before [4]. For MMC an open two-compartment model was assumed and the terminal half-life time ($t_{1/2}$) was obtained from a least squares regression analysis of the points belonging to the second phase ($t \geq 60$ min). The area under the plasma concentration vs. time curve (AUC) was determined with the trapezoidal rule till the last time point and the total body clearance (Cl_{tot}) was obtained by dividing the dose by the AUC. It was reported that using this procedure the obtained parameters did compare well with those obtained by using a non-linear curve fitting program [18]. The distribution volume V_d was calculated from $V_d = t_{1/2} \cdot Cl_{tot}/0.693$. An alternative approach based on system dynamics to calculate the model independent parameter mean residence time (MRT) was followed according to Ref. [18]. The renal clearance (Cl_{ren}) was obtained by dividing the total renal excretion by the AUC.

RESULTS AND DISCUSSION

In total 19 patients have been included in the study, among which nine males (median age 47, range 42–86) and 10 females (median age 44, range 27–71). The diagnosis was breast cancer [7], prostate cancer [3], cervical cancer [1], adenocarcinoma of unknown origin [4], cholangio carcinoma [1], stomach cancer [2] and pancreatic cancer [1].

From most of the patients two curves were obtained. The most important pharmacokinetic parameters for both groups are listed in Tables 1 and 2. Most of the patients did not show highly different curves after repeated administration of the drug and had similar plasma concentration–time curves as shown in Fig. 1. The mean values of the half-life time of the elimination phase ($t_{1/2}$), distribution volume (V_d), total body clearance (Cl_{tot}), renal clearance (Cl_{ren}) and mean residence time (MRT) values corresponded with previous reports [4, 7, 9]. The cumulative urinary excretion per cycle ranged from 0.2 to 22% for the single agent group and from 2 to 20% for the combination group. Variations in the duration of injection led to a missed peak-plasma concentration in some cases.

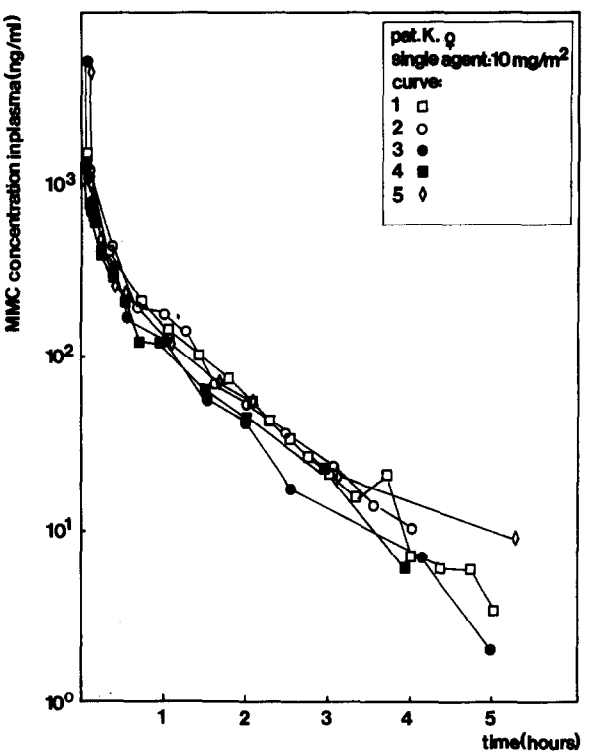

Fig. 1. Plasma concentration–time curve of MMC of patient K who received MMC as a single agent at a dose of 10 mg/m². *No differences between the five curves were observed.*

*Table 1. Pharmacokinetic parameters of patients receiving single agent MMC**

Patient	Curve No.	Dose (mg/m²)	$t_{1/2}$ (min)	AUC (μg.h/l)	V_d (l/m²)	Cl_{tot} (l/h.m²)	MRT (min)	Cl_{ren} (l/h.m²)	Urine (%)
U	1	12	62	496	36	24	46	2.0	8
	2	12	33	333	29	36	33	4.0	12
R	1	15	33	722	17	21	40	0.2	1
	2	15	33	496	24	30	35	—	—
	3	15	21	256	29	59	28	1.9	3
P	1	10	44	370	28	27	63	2.4	9
	2	10	53	563	23	18	40	2.2	12
	3	10	55	347	38	29	65	0.7	2
	4	10	53	265	48	38	63	4.0	11
Me	1	12	39	548	21	22	55	2.3	11
	2	13	79	722	37	18	74	2.8	16
	3	12	70	691	29	17	67	3.8	22
D	1	15	40	535	27	28	39	2.5	9
	2	15	45	386	42	39	31	1.7	4
Ma	1	13	51	732	22	18	54	0.2	1
	2	12.5	44	343	39	36	58	0.3	1
	3	10	40	360	27	28	58	0.4	1
K	1	10	51	609	20	16	47	3.2	20
	2	10	50	515	23	19	53	2.7	14
	3	10	43	492	21	20	40	2.9	14
	4	10	43	426	23	22	50	2.3	11
	5	10	71	529	32	19	56	1.1	6
Dr	1	15	26	622	10	16	38	—	—
	2	15	26	722	13	21	34	1.3	3
	3	15	31	321	36	47	27	—	—
HJ	1	15	47	494	35	30	41	1.2	4
	2	15	11	209	19	71	22	4.1	3
L	1	15	37	695	20	22	42	3.3	15
	2	15	26	362	27	43	30	2.9	7
	3	15	31	658	17	23	35	1.1	5
Mean†	1		43	446	23.6 ± 8.0	22.4 ± 4.9	46.5	1.9	8.7
	2		40	364	27.6 ± 9.2	33.1 ± 16.9	41.0	2.4	8.0

*$t_{1/2}$ = elimination half-life time; AUC = area under the plasma concentration–time curve; V_d = distribution volume; Cl_{tot} = total body clearance; MRT = mean residence time; Cl_{ren} = total renal clearance; urine % = percentage of administered dose excreted in the urine, collected till 4 h after injection.

†For the mean AUC values the MMC dose has been normalized to 10 mg/m², assuming linear pharmacokinetics at this range.

As a result, AUCs were artificially lowered by up to 15%. The $t_{1/2}$ is proportional to the ratio of the distribution volume and the clearance. For patient R (Table 1) both Cl_{tot} and V_d increased, each to varying extents, resulting in a net reduction of the $t_{1/2}$ during the three sequential courses (Fig. 2). All patients had normal liver and kidney functions and we were unable to explain the latter observations. Patient Me experienced an increase in $t_{1/2}$ (Fig. 3) when comparing the first with the later courses.

For the combination chemotherapy group a change in $t_{1/2}$ was also observed, as for patient S and patient Jo. These patients had normal kidney and liver functions. An overview of the variations in V_d and Cl_{tot} that occurred within a patient during repeated administration can be seen in Figs 4 and 5, respectively. The pharmacokinetic parameters of the first curve of each patient was set at 100%. Pharmacokinetic parameters of second and subsequent curves are expressed relative to those of the first curve. Large interindividual variations between the various pharmacokinetic parameters can be observed. An increase in Cl_{tot} was observed when comparing the first and the second dose. The mean values were 22.4 and 33.1 (single agent) and 22.6 and 27.2 (combination) for the first and the second injection, respectively, as expressed in l/h.m². This increase was significant for the single agent group ($P < 0.05$, using a paired t-test) and for the combination therapy group the difference was only significant at the $P = 0.2$ level. This increase may be explained by enhanced microsomal activity. This observation warrants further metabolism studies using hepatocytes. In the other parameters no significant differences between the mean values of first and second injection were observed. Although not statistically different the slight increase in the mean of V_d, when comparing

Table 2. Pharmacokinetic parameters of patients receiving combination chemotherapy

Patient	Curve No.	Dose (mg/m²)	$t_{1/2}$ (min)	AUC (μg.h/l)	V_d (l/m²)	Cl_{tot} (l/h.m²)	MRT (min)	Cl_{ren} (l/h.m²)	Urine (%)	Other agents*
M	1	6	43	476	13	13	38	1.9	15	V,B,P
	2	6	42	368	16	16	39	1.4	8	V,B,P
Mo	1	8	51	442	22	18	45	0.4	2	A
	2	8	53	395	26	20	50	1.7	8	A
J	1	10	35	271	31	37	47	7.0	19	A
	2	10	22	273	19	37	35	7.2	20	A
A	1	10	81	544	36	18	62	2.7	15	A
	2	10	76	603	37	20	67	1.9	10	A
	3	10	33	437	18	23	41	3.8	17	A
	4	10	41	353	28	28	48	—	—	A
	5	10	66	538	30	19	52	2.2	12	A
	6	10	45	519	21	19	49	1.0	5	A
S	1	10	55	421	31	24	56	3.2	13	A,5−F
	2	10	28	199	34	50	30	9.1	18	A,5−F
	3	10	86	312	60	29	73	3.4	12	A,5−F
Jo	1	10	46	493	22	20	49	2.0	10	VD
	2	10	97	358	65	28	61	2.7	10	VD
Z	1	10	33	257	31	39	32	3.5	9	A
	2	10	20	223	22	45	22	—	—	A
DJ	1	10	61	611	24	16	60	—	—	A,5−F
	2	10	87	744	28	13	69	—	—	A,5−F
B	1	10	55	558	24	18	52	—	—	A,5−F
	2	10	74	614	29	16	46	—	—	A,5−F
Mean	1		51	500†	26.0 ± 6.9	22.6 ± 19.3	49.0	3.0	11.9	
	2		55	458†	30.7 ± 14.5	27.2 ± 13.6	46.6	4.0	12.3	

*A = adriamycin; V = vincristine; Vd = vindesine; B = bleomycin; P = cisplatin; 5-F = 5-fluorouracil.
†Standardized for a dose of 10 mg/m².

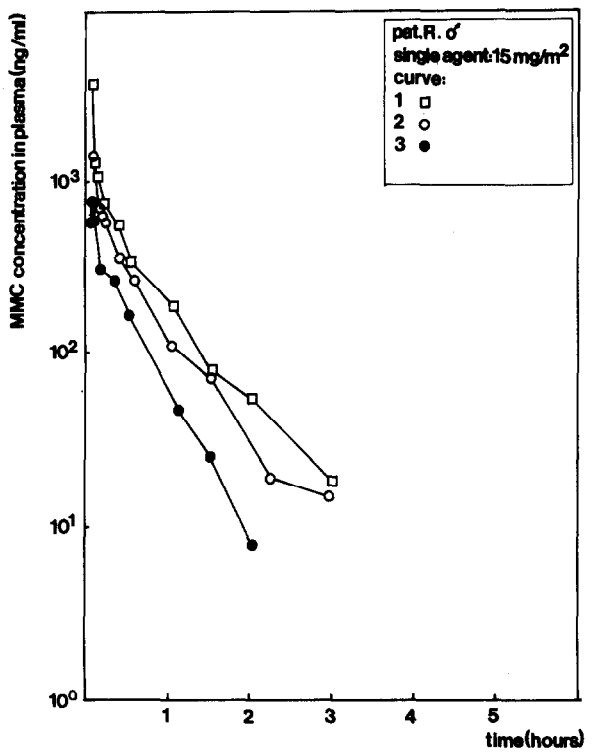

Fig. 2. Plasma concentration–time curve of MMC in patient R who received MMC as a single agent at a dose of 15 mg/m². *A decrease in the half-life of the elimination phase is observed:* $t_{1/2}$ (1) = 33 min, $t_{1/2}$ (2) = 33 min, $t_{1/2}$ (3) = 21 min. *This patient had normal liver and kidney functions.*

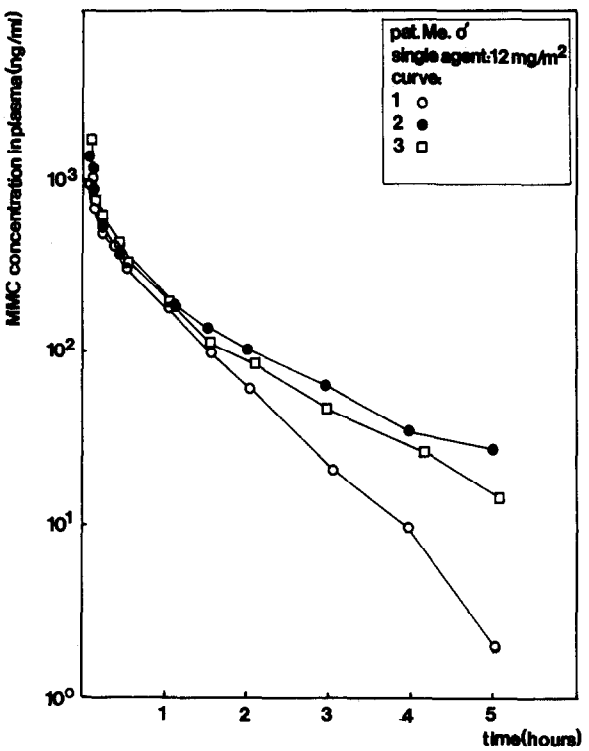

Fig. 3. Plasma concentration–time curve of MMC in patient Me (dose: 12 mg/m² *single agent). Kidney and liver functions were normal. An increase in* $t_{1/2}$ *was seen in the second and third curve:* $t_{1/2}$ (1) = 39 min, $t_{1/2}$ (2) = 87 min *and* $t_{1/2}$ (3) = 70 min.

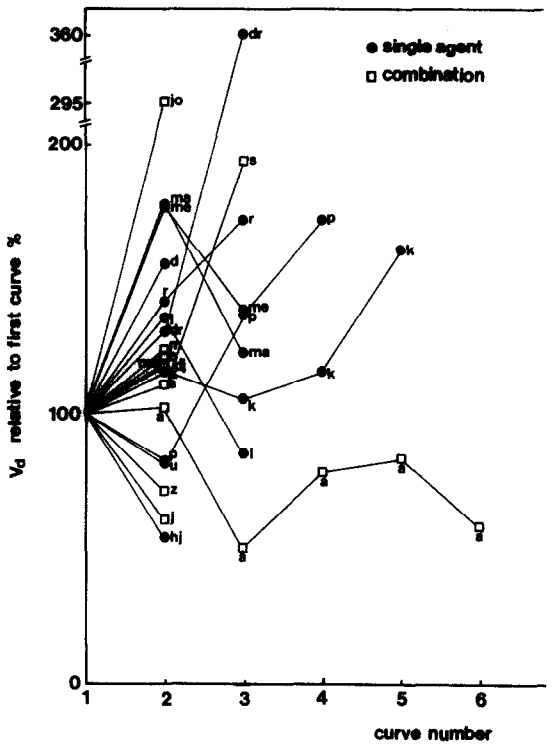

Fig. 4. Distribution volume V_d relative to first curve for all patients. Differences that occurred could not be related to liver or kidney toxicity.

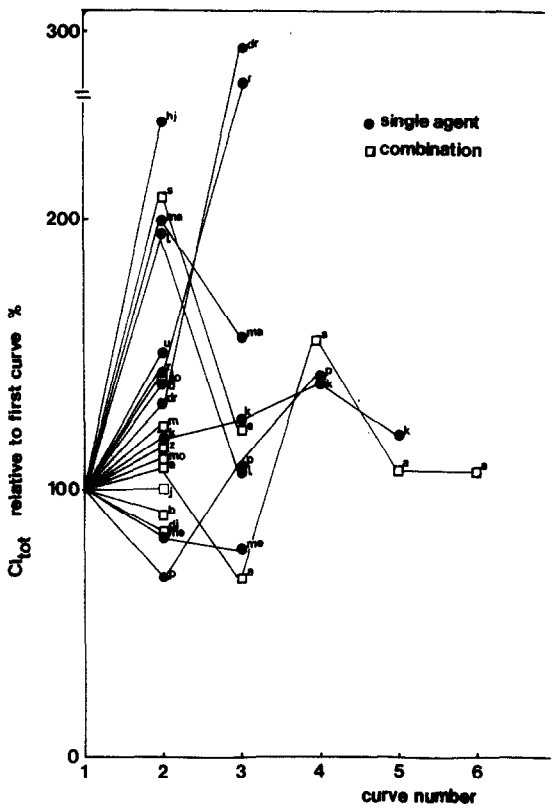

Fig. 5. Total body clearance (Cl_{tot}) relative to first curve. Patients with large differences between the first and subsequent curves showed no liver and/or kidney function disturbance.

the first and second injection, could be explained from a change in protein binding. The lower level of significance in the difference of the mean of Cl_{tot} for the combination therapy group may be due to the interference of other drugs. Although the primary aim of the presented study was not to evaluate toxicity in detail, the variations did not appear to correlate with clinical findings including blood cell count, renal function and liver function. In conclusion, the pharmacokinetic profiles of sequential courses of MMC failed to offer an explanation for the cumulative toxicity which tends to occur after repeated administration of MMC.

Acknowledgement—Helen Gall is gratefully acknowledged for collecting blood plasma samples of the patients.

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