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Pharmacokinetics of Bronchial Artery Infusion of Mitomycin in Patients with Non-small Cell Lung Cancer

Eiji Shimizu, Yoichi Nakamura, Jun-nosuke Mukai, Kenji Tani, Takashi Yamashita, Fumihiko Hojo, Yoshihiro Hashimoto and Takeshi Ogura

The pharmacokinetics of bronchial artery infusion of 20 mg (11.4–14.0 mg/m²) mitomycin was studied in 14 patients with non-small cell lung cancer (NSCLC). The mean elimination half-life was 34.3 min (range 6–72), and the area under the plasma concentration-time curve (AUC) was 166 ng h/ml (39–312). The mean maximum plasma drug concentration (C_{max}) was 178 ng/ml (12-540) and back-extrapolated plasma drug concentration was 308 ng/ml (17–1423). The mean volume of distribution in the one-compartment model was 0.183 l/kg (0.010–0.887) and the rate constant for unchanged drug appearing in the urine was 1.91/min (0.57–7.27). There was considerable variation among individuals with respect to the pharmacokinetics of mitomycin, and the mean C_{max} and AUC were lower than those reported after intravenous administration.
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INTRODUCTION

MITOMYCIN is one of the most active chemotherapeutic agents for non-small cell lung cancer (NSCLC) [1]. The pharmacokinetics of intravenous and intra-arterial mitomycin has been previously reported in patients with gastrointestinal malignancies [2–5]. However, no formal study of the pharmacokinetics of mitomycin after infusion into the bronchial artery, has been carried out in patients with NSCLC. We have done such a study.

PATIENTS AND METHODS

Patients

Plasma mitomycin concentrations were measured in 14 inoperable patients with NSCLC. Patients were entered for this study if they conformed to the following criteria: Eastern Cooperative Oncology Group (ECOG) performance status ≤3, leucocyte count ≥ 4000/μl and platelet count ≥100 000/μl, total serum bilirubin ≤3 mg/dl and aspartate aminotransferase (AST) less than twice the normal range, serum creatinine ≤1.5 mg/dl and 24-h creatinine clearance ≥30 ml/min. None of the patients had received chemotherapy or radiotherapy within 4 weeks before study. Informed consent was obtained from the patients.

Bronchial artery infusion and collection of blood samples

Before bronchial artery infusion, all patients had an intravenous cannula and heparin lock placed from which blood samples were collected, thus minimising the number of venipunctures. By Seldinger's method [6], an arterial catheter was inserted selectively in the bronchial artery feeding the tumour. 20 mg (11.4–14.0 mg/m²) mitomycin in 200 ml of saline was infused into the bronchial artery over 20 min. Blood samples were collected by puncture of the heparin lock with a needle attached to a plastic syringe containing heparin at 5, 20, 40, 60, 120 and 180 min after starting the infusion.

Assay of plasma mitomycin

The plasma was immediately separated by centrifugation and stored at −70°C. The plasma concentration of mitomycin was measured by bioassay using *Escherichia coli*. The sensitivity limit of the assay was 6.3 ng/ml.

Table 1. Pharmacokinetics of 20 mg mitomycin infused via bronchial artery

Patient	Bronchial artery	Dose (mg/m²)	C_{po} (ng/ml)	C_{max} (ng/ml)	$t_{1/2}$ (min)	K_{el} (/min)	V_d (l/kg)	AUC (ng h/ml)
1	Common	12.1	180	140	22	1.99	0.109	91
2	R	11.5	139	110	44	1.76	0.124	91
3	L	13.1	34	33	63	0.65	0.559	54
4	R	11.6	616	350	37	2.46	0.029	277
5	L	11.6	211	150	35	1.11	0.083	216
6	R	13.0	1423	540	6	7.27	0.010	277
7	L	13.5	368	260	34	1.21	0.061	268
8	R	12.0	17	12	72	0.57	0.887	39
9	R	13.2	409	300	27	1.54	0.041	312
10	L	11.6	372	200	17	2.47	0.042	191
11	L	11.4	154	100	25	1.68	0.094	126
12	L	14.0	50	41	27	1.55	0.318	40
13	R	13.8	144	130	42	0.99	0.102	196
14	R	13.7	195	130	29	1.43	0.098	142
Mean			308	178	34.3	1.91	0.183	166
(S.D.)			(348)	(138)	(16.6)	(1.59)	(0.24)	(92)

R = right, L = left.

Correspondence to E. Shimizu, NCI-Navy Medical Oncology Branch, National Cancer Institute, Building 8, Room 5101, Bethesda, Maryland 20889-5105, U.S.A.
The authors are at the Third Department of Internal Medicine, The University of Tokushima School of Medicine, 3-18-15 Kuramoto-cho, Tokushima 770, Japan.
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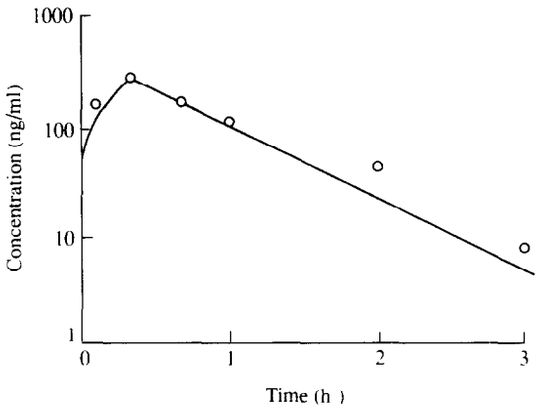

Fig. 1. Plasma mitomycin concentrations following bronchial artery infusion of 20 mg in patients with NSCLC.

Calculations

All pharmacological parameters were calculated assuming a one-compartment model. The area under the plasma concentration-time curve (AUC) for mitomycin was determined by trapezoidal approximation up to the last observation, and then extrapolated by dividing the final concentration by the elimination rate constant (K_{el}). Linear least-squares regression analysis was used to calculate K_{el}, and the biological half-life ($t_{1/2}$) was calculated by dividing 0.693 (constant) by K_{el}. The volume of distribution (V_d) and the initial plasma concentration were calculated from these parameters: AUC, total plasma clearance (Cl_{total}) and K_{el}. Then, V_d was determined by dividing Cl_{total} by K_{el} and the initial plasma concentration (C_{po}) just after the infusion was calculated by dividing the dose in the body (D_o) by the calculated V_d.

RESULTS

20 mg mitomycin was administered via the bronchial artery in all our patients with NSCLC (Table 1). The body surface area of the patients varied between 1.43 and 1.75 m^2 (median 1.60). The dose per surface area varied between 11.4 and 14.0 mg/m^2. Bronchial arteries supplying the primary lung cancer were on the right in 7 patients and on the left in 6 patients. The common bronchial artery was in 1 patient.

There was a 12-fold variation in both the $t_{1/2}$ of mitomycin (range 6–72 min) and K_{el} (0.57–7.27/min). A 45-fold variation occurred in C_{max} (12–540 ng/ml). An 84-fold variation occurred in C_{po} (17–1423 ng/ml), while an 8-fold variation occurred in AUC (39–312 ng h/ml). An 89-fold variation was observed in V_d (0.010–0.887 l/kg). There was considerable variation between individuals. Figure 1 shows a representative curve of plasma mitomycin after a 20 min infusion via the bronchial artery. C_{max} was observed typically at 20 min after the start of the infusion.

DISCUSSION

Mitomycin is an antineoplastic drug with single-agent activity in NSCLC. Selawry [7] reviewed three papers and reported a 23% response rate in 185 NSCLC patients. Two more recent phase II trials demonstrated a 27% response rate in 55 NSCLC patients [8, 9]. Combination chemotherapy including mitomycin has had response rates of 10–60% [1, 10–14] but the role of combination chemotherapy to prolongation of survival time of NSCLC patients is controversial.

In 1963 chemotherapeutic drugs were infused selectively into a bronchial artery by Boijsen *et al.* [15] in an attempt to treat lung cancer. Similar attempts were also made by Kahn *et al.* [16], Haller *et al.* [17], and Nordenstrom [18]. The advantage of bronchial artery infusion is the potential for increasing the exposure of the tumour to the drug while avoiding systemic toxicity. In 1969, Neyazaki *et al.* [19] attempted preoperative infusion of mitomycin via the bronchial artery. They treated 27 patients with 10–40 mg mitomycin and the tumours were resected in 14 patients, of whom 5 survived longer than 2 years. In 1975, Ogata and Yoneyama [20] reported promising results after bronchial artery infusion of mitomycin. Similar promising results were also obtained by Hellekant *et al.* [21, 22] and Ekholm *et al.* [23, 24]. Recently, we reported a phase II evaluation of the technique with only slight systemic toxicity [25]. This pharmacokinetic study was undertaken during that phase II study.

The mean $t_{1/2}$ (34 min) was shorter than that reported in previous studies (range 23–116; mean 48 mg/m^2) of intravenous mitomycin administration (6.5–20 mg/m^2) [26]. Kato *et al.* [2] reported a mean $t_{1/2}$ of 64 min during upper rectal artery infusion of mitomycin (20 mg). Furthermore, we found that the $t_{1/2}$ after bronchial artery infusion varied widely by 12-fold. The mean C_{max} (178 ng/ml) was lower than that reported previously (700–6000 ng/ml) when mitomycin (6.5–20 mg/m^2) was infused intravenously [26]. Kato *et al.* [2] reported a mean C_{max} of 830 ng/ml when 20 mg mitomycin was infused into the upper rectal artery. In our study, C_{max} varied 45-fold .

We obtained an AUC of 166 ng h/ml which was lower than that reported previously (range 138–1222; mean 617) for intravenous administration of 6.5–20 mg/m^2 mitomycin [26]. Kato *et al.* [2] reported that the mean AUC obtained by upper rectal artery infusion of 20 mg mitomycin was 417 ng h/ml. In our study, the AUC varied 8-fold.

The differences in these pharmacokinetic parameters between the present study and previous reports may be related to the route of administration, dose of drug or liver function. During intra-arterial administration, drugs may be extracted extensively by regional tumour cells or tissue, thereby significantly enhancing localization of chemotherapeutic drugs and reducing systemic exposure (AUC) to the drug. Any reduction of drug delivery to either the bone marrow or other important organs may greatly reduce side-effects such as myelosuppression. Fujita [27] proposed that mitomycin has a dose-dependent disposition in man and suggested that longer half-lives were seen with higher doses. The variation among individuals of $t_{1/2}$ seen in this study may also be explained by variation in uptake by regional tumour cells, and therefore variable systemic delivery. Only a small fraction of the mitomycin dose is excreted unchanged in the urine (less than 20%), and altered renal function does not affect the elimination of the drug significantly [3, 4]. Most of the drug is excreted in the bile and the fact that mitomycin levels are higher in bile than in plasma suggests that the drug may be recycled enterohepatically *in vivo* [5]. In this study, however, there was no correlation of pharmacokinetic parameters and liver function tests (data not shown).

In conclusion, the pharmacokinetic profile after bronchial artery infusion of mitomycin varied widely among individuals and the mean C_{max} and AUC were lower than those reported previously for intravenous administration of the drug [26].

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