Eur J Cancer Clin Oncol, Vol. 22, No. 11, pp. 1309–1314, 1986.
Printed in Great Britain

0277-5379/86$3.00+0.00
Pergamon Journals Ltd.

Intrahepatic Arterial Administration of 4'Epidoxorubicin (Epirubicin) in Advanced Cancer Patients. A Pharmacokinetic Study

FRANCO PANNUTI,* CARLO M. CAMAGGI,† ELENA STROCCHI,* RAFFAELLA COMPARSI,* ANDREA P. ROSSI,* BRUNA ANGELELLI* and ANTONELLO FRANCHINI‡

**Divisione di Oncologia, Ospedale M. Malpighi, Via Albertoni, 15 – Bologna; †Istituto di Chimica Organica, Viale Risorgimento, 4 Bologna, and ‡Istituto di Patologia Speciale Chirurgica e Semeiotica Chirurgica, Bologna, Italy*

Abstract—*Epirubicin (epiDX) pharmacokinetics was followed in 10 advanced cancer patients with hepatic metastases from colorectal carcinoma or primary liver tumor after single bolus administration (20–40 mg) in the hepatic artery, through a surgically implanted catheter and subcutaneous access port. EpiDX plasma and whole blood concentrations follow a triphasic decay qualitatively similar to that observed after IV administration. Blood levels are consistently higher than plasma levels. Plasma clearance (nine patients, mean: 93.4 l/hr; range: 69.3–129.5 l/hr) is higher than the corresponding parameter determined in patients with hepatic metastases after intravenous therapy. The remaining patient is characterised by an abnormally low plasma clearance (13.6 l/hr), due to a hepato–pulmonary shunt. The subjects in this study were exposed to very low drug concentrations, and therefore experienced no relevant adverse side-effects.*

INTRODUCTION

CATHETERIZATION of the hepatic artery and intrahepatic (IA) administration of doxorubicin (DX) in non-resectable liver malignancies has been studied by several authors. Equivalent drug disposition has been reported for doses given intravenously into a peripheral vein or directly into the hepatic artery [1, 2, 4]. The incidence of side-effects seems to be similar also. Some controversy exists on the hepatic extraction ratio of DX, recently reported to be very low, less than 0.1 [1], at variance with the previously reported results [3]. Overall, the published data demonstrate there are no advantages for intra-arterial doxorubicin therapy over standard intravenous therapy.

Epirubicin (4'epidoxorubicin, epiDX) might be a better candidate for intrahepatic arterial administration. EpiDX plasma clearance is definitely higher than DX clearance, and related to hepatic blood flow [5]; biliary and urinary excretion data indicate that the drug metabolism is mainly hepatic [6, 7]. Even in patients with impaired liver functions and hepatic metastases, epirubicin plasma clearance is about 30–40% of the liver blood flow, a value not too far from that observed for doxorubicin in patients with normal liver functions [8].

A clinical trial on the efficacy of intrahepatic arterial treatments with epiDX and 5–fluorouracil in patients with advanced liver metastases or primary tumor is currently in progress in our institute. We report here on the results obtained in 10 of these subjects concerning the pharmacokinetic behaviour of the new anthracycline antibiotic epirubicin.

MATERIALS AND METHODS

Patients

The subjects in this study were 10 advanced cancer patients enrolled in a clinical trial concerning the efficacy of intrahepatic arterial administration of epirubicin and 5–fluorouracil in the management of unresectable liver malignancies. Eligibility criteria were:

a. Non-resectable histologically documented hepatocarcinoma or hepatic metastases from colorectal cancer, with the absence of documented extrahepatic involvement.
b. Bilirubin level < 2 mg/dl, SGOT < 120 U/l, Albumin > 2 g/dl.
c. Age <70 yr.

Accepted 3 February 1986.
Supported in part by contract CNR, no.84.00710.44 (Progetto Finalizzato 'Oncologia', Italian National Council of Research).

Table 1. Patient characteristics

Pts	Tumor	Metastases	Age (yr)	Wt (kg)	Perf.st. (%)
#47	Rectum	LI	72	59	50
#59	Liver	LI	43	51	50
#51	Colon	LI,ST	57	63	40
#3	Breast	LI,ST	48	67	40
#37	Liver		56	58	50
#39	Colon	LI	66	66	90
#41	Rectum	LI	53	76	70
#42	Colon	LI	36	52	50
#45	Peritoneum	LI,PE	37	87	70
#50	Rectum	LI	63	61	70

LI: Liver, ST: Soft Tissues, PE: Peritoneum.
Perf.st.: Karnofsky Performance status (%).

Baseline data for the patients entered in the pharmacokinetic study are reported in Table 1.

Drug administration

A Sylastic catheter, connected to a subcutaneous access (Infuse Access Port model) was surgically implanted in the hepatic artery via the gastroduodenal artery. A preoperatorial arteriographic study of the celiac and superior mesenteric arteries gave the anatomical basis for a correct implantation [9].

Hepatic perfusion was controlled by comparison of scintigraphic images obtained before (3.0 mCi of 99Tc—sulfur colloid IV) and after surgery (99Tc MAA injected through the subcutaneous access port) [10].

EpiDX was administered by rapid infusion (2–3 min) through the access port, after a preliminary washing of the cathcter with saline (10 ml). After the treatment, the catheter was once again washed first with saline (10 ml), and then with a heparinized saline solution (5 ml). In three patients (#47, #57, #59) a cross-over experiment was carried out by administering epiDX in subsequent cycles by the IA and intravenous (IV) routes. Blood samples (4 ml) were drawn before and 15, 30, 60 min, 2, 3, 4, 6, 8, 10, 24, 48, 72, 96, 120 and 144 hr after the treatment.

Urine was continuously collected and total diuresis was registered at regular intervals; samples were kept frozen at − 20° C in light protected tubes until analysis.

After the preliminary pharmacokinetic study with epiDX alone, the treatment was continued following a weekly schedule involving the intrahepatic administration of epiDX (40 mg) and 5–fluorouracil (750 mg).

EpiDX analysis

Plasma and whole blood levels of epiDX and its reduced metabolite epirubicinol were determined following a High Pressure Liquid Chromatographic method [8]. In order to achieve sufficient sensitivity, the analytical procedure previously described was slightly modified as follows.

Plasma

One hundred microlitres of a stock solution of daunorubicin hydrocloride as internal standard, 1 ml of phosphate buffer (pH 8) and 10 ml of chloroform–heptanol (9 : 1) were added to plasma samples (1–3 ml). The mixture was shaken for 5 min in a vortex mixer and then centrifuged. The organic layer was collected and extracted with 0.5 ml of 0.3 M phosphoric acid in a vortex mixer. The acidic phase, after treatment with 2 ml of *n*-hexane to remove nonpolar contaminants, was analysed by HPLC (10–100 µl injections). This method — calibrated in the usual way by analysing blood bank plasma samples spiked with known amounts of epiDX and metabolites — is useful in the presence of very low drug levels (as low as 0.2 ng/ml; 3 ml of plasma extracted) but does not allow the determination of glucuronated metabolites.

Blood

Blood samples (1–3 ml) were added of 100µl of a stock solution of internal standard, 1 ml of phosphate buffer (pH 8) and 1 ml of methanol; the mixture was sonicated for 10 min, then centrifuged. The surnatant was then processed as described for plasma samples.

Urine

Urine samples (1 ml) were both extracted — following the procedure described above for plasma samples — or directly injected in the chromatographic system after addition of the internal standard and dilution with 1 ml of distilled water and 1 ml of 0.3 M phosphoric acid.

Chromatographic analysis

Chromatographic analysis was performed with a Varian model 5000 liquid chromatograph equipped with a Perkin–Elmer 650–10LC fluorescence detector (excitation wave length : 470 nm, emission : 580 nm) and a Supelco LC-CN chromatographic column (25 cm × 4.6 i.d.). Mobile phase consisted of acetonitrile : water (0.03 M phosphoric acid, 0.01 M KH2PO4) 25 : 75. Quantitation was performed with a Varian Vista 401 data system.

Computational methods

Pharmacokinetic analysis was performed by following both the classical multicompartment analysis and Statistical Moment Theory [11].

Plasma and whole blood decay curves were fitted with poliexponential equations:

$$C = \sum_{i=1}^{n} \text{Ai.Exp}[-\alpha i.t]$$

using the PAR program of the BMDP—Biomedical computer programs—University of California [12].

Model independent parameters were computed as follows, using, if available, both plasma and blood concentration data:

Plasma (or blood) clearance : $PlCl = \text{Dose}/\int Cdt$

Mean residence time : $MRT = \int tCdt/\int Cdt$

Apparent volume of distribution :
$Vss = PlCl.MRT$

Renal clearance was obtained by determining the concentration of the drug in urinary excretion:

Renal clearance : $RCl = [Xu]/\int Cdt$

where $[Xu]$ is the amount of unmetabolised drug eliminated in the urine during the time interval $t1$ to $t2$.

The pharmacokinetic discussion will be limited to model-independent parameters (with the exception only of the terminal half-life values, reported for comparison with other works). Complex multicompartmental systems are prone to be not uniquely defined, as structural identification can demonstrate. In addition, cross-over experiments involving different administration routes are better interpreted using model-independent parameters.

RESULTS

After intrahepatic arterial administration, epiDX plasma and whole blood levels follow a triphasic decay qualitatively similar to that observed after intravenous treatment (Fig. 1). Patient #37 is characterized by abnormally high plasma levels; the lack of an efficient hepatic first pass effect was explained by an hepatic arteriogram showing a hepato-pulmonary shunt.

EpiDX blood levels are consistently higher than plasma levels, in accordance with our observations following IV treatments.

The concentration of the C–13 reduced metabolite epirubicinol reaches a peak immediately after the drug administration. A biphasic decay then follows with an apparent half-life similar to that of the parent drug. The ratios between areas under the time–concentration curves relative to epirubicinol and epirubicin show that the hydroxylated metabolite is less bound to blood cells than the parent drug.

In three patients it was possible to carry on a cross-over experiment administering epirubicin both by the intravenous and intrahepatic arterial routes.

Table 2 reports pharmacokinetic parameters computed in the usual way according to statistical moment theory. In two of these patients plasma and blood clearances determined after intrahepatic arterial administration are consistently higher than the corresponding parameters determined after IV treatment. The third patient is characterized by a relatively high plasma clearance even after IV bolus, notwithstanding the presence of a primary liver tumor. Even in this patient, however, blood clearance is nevertheless definitely higher after IA treatment.

Pharmacokinetic parameters for the remaining patients are reported in Table 3. Patient #37 was previously shown to have a hepatopulmunary shunt, and this prevents an efficient liver first pass-effect, as shown by the clearance parameter. The remaining patients show quite a high plasma clearance, sometimes well in excess of the normal blood flow through the liver. No significant dependence of clearance parameters on the administered dose can be observed.

Interpatient variability in parameters as *MRT* and *Vss* are unfortunately not surprising. These pharmacokinetic parameters are obtained from the first moment of the time–concentration curve, and are obviously prone to be affected even by minor experimental errors in patients with such a low drug concentration.

Renal clearance was also measured in six patients, and was rather constant in five of these subjects (4.4–6.7 l/hr, mean: 5.4 l/hr).

DISCUSSION

In our opinion, intrahepatic arterial administration of epiDX is worth extensive clinical trials.

The pharmacokinetic behaviour of this drug reflects the basic requirements for this loco-regional therapy. EpiDX is efficiently metabolised

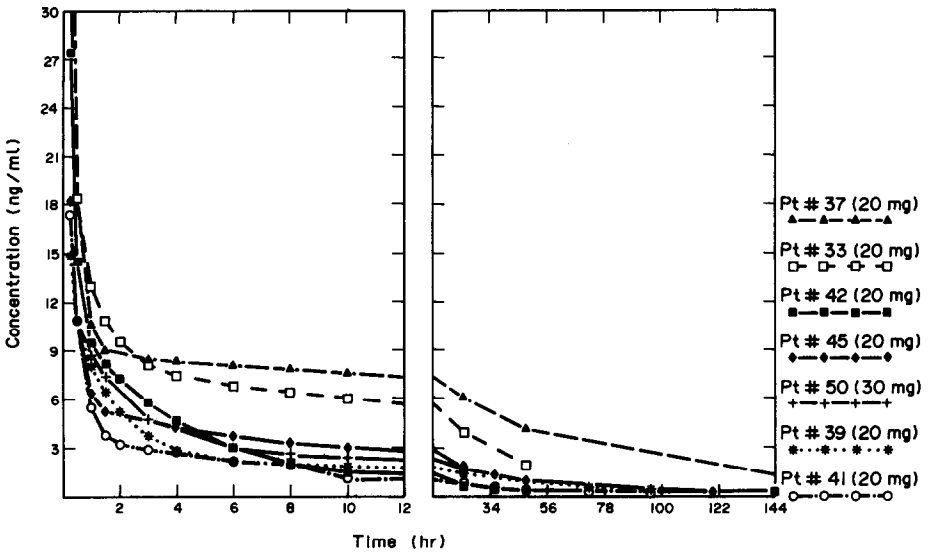

Fig. 1. Epirubicin plasma levels observed in seven patients after intrahepatic artery administration.

by the liver, and is quickly removed from the plasma toward blood cells and extravascular compartments. The direct introduction into the hepatic artery, the main artery responsible for blood supply to liver tumours, guarantees high bioavailability of free drug at the tumour site. Both hepatic metabolism and blood cells complexation then remove the drug from plasma, with consequent lower systemic toxicity.

Our results on the epirubicin pharmacokinetics reinforce the basic therapeutic requirements: integrity of liver functions and accurate anatomical study before and after the insertion of the catheter. The literature actually shows that failures of DX loco-regional therapies are more often encountered in cirrhotic patients. The presence of an arterial shunt, which allows part of the drug to bypass the liver, might be in addition an exclusion criterion

Table 2. Epirubicin pharmacokinetics after intrahepatic artery (IA) or intravenous bolus administration (IV)

Patient		Administration	*Cl* (l/hr)	*MRT* (hr)	*Vss* (l/kg)	*t*/2 (hr)	*t*/2 ol (hr)	*AUC*ol/*AUC*
#47	– Blood	40 mg – IA	40.8	66.9	46.2	61.6	50.1	0.20
	– Plasma		74.8	24.0	30.5	53.8	45.2	0.24
#47	– Blood	50 mg – IV	21.3	18.5	6.5	30.9	27.6	0.12
	– Plasma		36.1	14.4	8.8	31.9	30.1	0.16
#59	– Blood	30 mg – IA	47.2	43.5	40.0	50.5	52.5	0.16
	– Plasma		79.3	36.1	49.7	34.9	40.5	0.26
#59	– Blood	50 mg – IV	35.8	54.5	38.1	41.7	48.4	0.12
	– Plasma		73.8	37.9	54.6	34.8	43.8	0.35
#51	– Blood	20 mg – IA	30.2	69.8	33.5	66.7	58.8	0.17
	– Plasma		84.2	68.9	92.2	67.9	47.3	0.56
#51	– Blood	40 mg – IV	23.5	88.6	33.1	61.7	61.5	0.19
	– Plasma		36.5	88.6	51.4	67.6	65.3	0.52
Mean	– Blood	IA	39.4	60.1	40.0	59.6	53.8	0.18
	– Plasma		79.4	43.0	57.5	52.2	44.3	0.35
Mean	– Blood	IV	26.9	53.9	25.9	44.8	45.8	0.14
	– Plasma		48.8	47.0	38.3	44.8	46.4	0.34

MRT : Mean residence time.
Cl : Plasma (PlCl) or Blood (BlCl) clearance.
Vss : Volume of distribution at steady state.
t/2 : half-life of drug. *T*/2 ol: half life of hydroxilated metabolite.
*AUC*m/*AUC* : ratio between area under the time-concentration curve (*AUC*) of OH-metabolite and *AUC* of the unaltered drug.

Table 3. Epirubicin pharmacokinetics after intrahepatic artery administration (IA).

Patient	Administration	*PlCl* (l/hr)	*MRT* (hr)	*VSS* (l/kg)	*t/2* (hr)	*t/2* ol (hr)	*AUCol/AUC*	*Rcl* (l/hr)
#33	20 mg – IA	69.3	29.3	30.3	22.4	22.0	0.35	4.4
#37*	20 mg – IA	13.6	22.4	5.2	42.3	41.3	0.30	4.4
#39	20 mg – IA	111.4	33.3	56.2	36.3	40.1	0.37	5.9
#41	20 mg – IA	96.8	21.3	27.3	29.3	27.1	0.31	6.7
#42	20 mg – IA	74.7	40.1	57.1	35.8	34.8	0.28	25.0
#45	20 mg – IA	129.5	37.5	80.8	26.0	32.4	0.41	5.5
#50	30 mg – IA	120.4	35.1	69.3	30.8	34.2	0.47	/
#47†	40 mg – IA	74.8	24.0	30.5	53.8	45.2	0.24	/
#59†	30 mg – IA	79.3	36.1	49.7	34.9	40.5	0.26	/
#51†	20 mg – IA	84.2	68.9	92.2	67.9	47.3	0.56	/
Mean*		93.4	36.2	54.8	37.5	36.0	0.36	5.6‡
S.D.		20.9	13.0	21.8	13.6	7.8	0.10	0.9

*Mean values relative to nine patients (patient #37 has a hepato-pulmonary shunt and was excluded).
†pts from table 1.
Patient #42 excluded.
‡*PlCl*: Plasma Clearance. *MRT*: Mean Residence Time. *Vss*: Volume of distribution at steady state. *t/2*: half-life of drug. *t/2*: ol; half-life of OH-metabolite. *AUCol/AUC*: ratio between the area under the time-concentration curve (*AUC*) of OH-metabolite and AUC of the drug. *RCl*: renal clearance.

for intrahepatic therapy, as indicated by the pharmacokinetic results seen for patient #37. No definite evidences of kinetic non-linearity were found in this study in the 20–40 mg dosage range. This notwithstanding, it must be remembered that an increase of the administered dose can well saturate the hepatic metabolism, and prevent an efficient first pass effect.

Complete clinical results of the currently ongoing protocol involving weekly intrahepatic arterial treatment of liver malignancies with 5–fluorouracil (750 mg) and epirubicin (40 mg) will be reported elsewhere. Preliminary results on the toxicity of the treatment are of relevance for this paper and will be briefly reviewed.

On a total of 393 cycles (17 patients, follow-up 4–28 months), mild leukopenia (grade 1 WHO) occurred only in 12 cycles. Vomiting (grade 2 WHO) occurred in 5 cycles. No other relevant side effects were observed. Only pt. #37, bearing a hepato–pulmonary shunt was subjected to slightly worse side-effects (leukopenia, grade 1 WHO, 4/30 cycles, and alopecia, grade 1 WHO).

No clinical or electrocardiographic evidence of cardiac injury was observed. No significant alteration in left ventricular ejection fraction (LVEF) was observed by angiocardioscintigraphy, performed in the patients (5/17) who received a cumulative epiDX dosage in excess of 700 mg/m^2. Presently, these subjects have been exposed to a total of 1325, 925, 900, 769 and 750 mg/m^2 of epiDX.

REFERENCES

1. Ballet F, Barbare C, Poupon R. Hepatic extraction of Adriamycin in patients with hepatocellular carcinoma. *Eur J Cancer Clin Oncol* 1984, **20**, 761–764.
2. Bern MM, McDermott W Jr, Cady B, Oberfield RA, Trey C, Clouse ME, Tullis JL, Parker LM. Intraarterial hepatic infusion and intravenous Adriamycin for treatment of hepatocellular carcinoma. *Cancer* 1978, **42**, 399–405.
3. Garnick MB, Ensminger WD, Israel M. A clinical–pharmacological evaluation of hepatic arterial infusion of Adriamycin. *Cancer Res* 1979, **39**, 4105–4110.
4. Lee YTN, Chan KK, Harris PA, Cohen JL. Distribution of Adriamycin in cancer patients. Tissue uptakes, plasma concentration after IV and I.A. administration. *Cancer* 1980, **45**, 2231–2239.
5. Camaggi CM, Strocchi E, Martoni A, Angelelli B, Comparsi R, Pannuti F. Epirubicin plasma and blood pharmacokinetics after single IV Bolus in advanced cancer patients. *Drugs Exptl Clin Res* 1985, **XI(4)**, 285–294.
6. Camaggi CM, Strocchi E, Comparsi R, Angelelli B, Pannuti F. Biliary excretion of 4' epidoxorubicin in advanced cancer patients. *Cancer Chemother Pharmacol* 1986 (in press).
7. Cassinelli G, Configliacchi E, Penco S. *et al.* Separation, characterization and analysis of epirubicin (4'-Epidoxorubicin) and its metabolites from human urine. *Drug Metabolism and Disposition* 1984, **12**, 4–20.

8. Camaggi CM, Strocchi E, Tamassia V. *et al.* Pharmacokinetic studies of 4'epidoxorubicin in cancer patients with normal and impaired renal functions and with hepatic metastases. *Cancer Treat Rep* 1982, **66**, 1819–1824.
9. Cohen AM, Franchini A, Del Prete P. Regional Hepatic Chemotherapy using a totally implantable drug delivery system for the treatment of primary and metastatic cancer of the liver: literature review and our experience. *Giorn Chir* 1983, **4**, 383–391.
10. Kaplan WD, Ensminger WD, Come SE. *et al.* Radionuclide angiography to predict patient response to hepatic artery chemotherapy. *Cancer Treat Rep* 1980, **64**, 1217–1222.
11. Gibaldi G, Perrier D. *Pharmacokinetics* 2nd edn. New York, Marcel Dekker, 1972.
12. Dixon WJ, Brown MB: *BMDP–79 Biomedical Computer Programs, P-series.* Berkeley, University of California Press, 1979.