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Decreased Half Life of Cyclophosphamide in Patients Under Continual Treatment*

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Abstract—*Plasma levels of cyclophosphamide (Cy) were measured in 16 cancer patients receiving 100 mg/day of Cy for over 1 yr. Oral and intravenous administrations gave similar AUC values, confirming that intestinal absorption is almost complete. When pharmacokinetics obtained at the first course of therapy were compared with pharmacokinetics measured after more than 6 months continual treatment, $T\frac{1}{2}$ and Vd appeared significantly lower in the second population despite broad variability among patients.*

INTRODUCTION

CYCLOPHOSPHAMIDE (Cy) is metabolized into active derivatives by liver microsomal enzymes [1–6]. Its activation is increased in phenobarbital induced animals [7], and inducing activity has also been shown in animals [8].

In clinical practice Cy is employed in several regimens, from refracted high doses to continued low doses. In ovarian cancer, these two schedules offer similar efficacy, although the continual low doses seem to be less toxic [9]. However, responders to this type of treatment eventually become resistant—after varying lengths of time—and it remains to be seen whether cellular resistance to alkylating agents or altered metabolization and excretion of the drug is responsible.

The aim of this study is to check whether after prolonged treatment with Cy there is any change in the rate of disappearance of the drug.

MATERIALS AND METHODS

Patients

Sixteen patients, aged from 44 to 75 yr, with normal liver and renal function, were suffering from gynecological malignancies. They had never been treated before with antitumoral agents and were taking no other drugs.

A first group of 9 patients was studied during their first course of therapy with 100 mg/day of Cy. Eight of these patients were studied for gastrointestinal absorption, by comparing the area under the curve (AUC) obtained after an intravenous bolus with the AUC after oral administration of the same dose. Patients receiving the drug orally fasted from 10 hr before till 5 hr after the treatment.

A second group of 9 patients treated for 6–13 months with the 100 mg/day regimen was studied after they had stopped treatment for 2 days. In this group 7 patients had been under continual treatment for between 10 and 13 months, and 2 were only at the sixth month of treatment and had been evaluated previously in the first group.

A total of 8–10 samples of 3 ml of blood were taken from each patient during the 24 hr following administration. Blood was transferred to heparinized tubes at 4°C and spun down at 1500 ***g***; plasma was stored at −20°C. After double extraction in ethyl acetate the samples were redissolved in ethanol and injected into a Fractovap 2300 (Carlo Erba) gas chromatograph with a 2 m glass column packed with 100–120 mesh Gas Chrom Q coated with OV 17 3%, and equipped with a NPSD detector. This method, based on the selective sensitivity

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of the NPSD detector to nitrogen and phosphorus, is described in detail elsewhere [14].

Statistical analysis was by the non-parametric test of Mann–Whitney because of the wide dispersion of the data.

RESULTS

Oral low dose cyclophosphamide treatment produces measurable levels of the drug with peaks in the range of 1 μg/ml and an AUC very close to that after i.v. injection, with a mean ratio AUC p.o./AUC i.v. of 0.97 (Table 1). Comparing the half life ($T\frac{1}{2}$) and the volume of distribution (Vd) of the drug at the beginning of therapy and after prolonged treatment (Table 2), the variability among patients is large and both $T\frac{1}{2}$ ($P<0.05$) and Vd ($P<0.01$) are

Table 1.

Patient	Body weight (kg)	$T\frac{1}{2}$ hr	i.v.* AUC μg/ml . min	p.o.* AUC μg/ml . min	Peak level μg/ml	Peak level min	24 hr level μg/ml
TI	74	5.2	662	687	1.20	225	0.10
BI	47	10.3	1546	1146	1.44	267	0.30
FE	80	7.4	881	754	0.95	360	—
IG	46	5.1	837	803	1.38	360	0.15
TE	48	10.7	1800	1372	1.68	420	0.35
RL	56	7.8	1040	995	1.19	300	0.13
ML	52	6.6	696	906	1.30	252	0.17
PC	61	6.1	411	526	0.79	255	0.08

*100 mg cyclophosphamide.

Table 2.

Patient	Age	Weight kg	Diagnosis	Months of therapy	$T\frac{1}{2}$ hr	Vd l
TI	52	74	Ovarian cancer	0	5.19	65
BI	63	47	Ovarian cancer	0	10.29	61
FE	44	80	Ovarian cancer	0	7.37	68
IG	48	46	Ovarian cancer	0	5.10	53
TE	45	48	Ovarian cancer	0	10.69	52
RL	75	55	Ovarian cancer	0	7.82	44
TA	76	57	Ovarian cancer	0	6.90	28
ML	75	52	Vaginal urotelioma	0	6.64	86
PC	64	61	Genital sarcoma	0	6.06	116
					$T\frac{1}{2}$ =7.33	Vd =63.66
					S.E. =0.66	S.E. = 8.47
					Median $T\frac{1}{2}$ =6.30	Median Vd =61
TI	52	73	Ovarian cancer	6	3.64	26
BI	63	47	Ovarian cancer	6	6.20	39
MO	21	50	Ovarian cancer	10	3.70	20
RO	44	60	Ovarian cancer	11	2.72	19
BA	66	75	Ovarian cancer	13	5.86	32
SS	58	61	Ovarian cancer	13	5.00	61
FD	22	56	Ovarian cancer	10	3.53	40
FA	61	63	Ovarian cancer	13	3.63	33
SA	72	59	Ovarian cancer	12	9.60	20
					$T\frac{1}{2}$ =4.87	Vd =32.22
					S.E. =0.7	S.E. = 4.48
					Median $T\frac{1}{2}$ =3.70	Median Vd =32

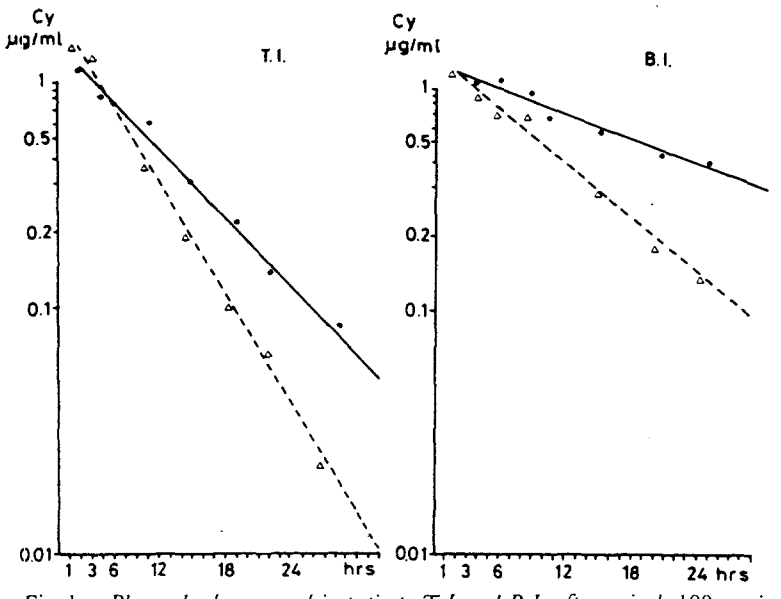

Fig. 1. Plasma levels measured in patients T.I. and B.I. after a single 100 mg *i.v. injection of Cy.* ● *First dose:* △ *Last dose after six months continual treatment.*

lower in long-treatment patients. In the 2 patients who were evaluated at the beginning and after 6 months of continual treatment, the $T\frac{1}{2}$ is shorter (Fig. 1). The volumes of distribution show the same trend in both the twice tested patients and the two groups of 7 patients.

DISCUSSION

As shown in previous studies, Cy is absorbed very well by the gastrointestinal tract and its rate of disappearance from plasma varies widely from one subject to another [15]. This probably reflects individual differences in the activity of liver microsomal enzymes. The range of individual variability recorded by us as by previous workers is certainly responsible for the difficulties in detecting alterations in Cy metabolism due to repeated treatment in detecting alterations in Cy metabolism due to repeated treatments. Our data, however, show a significant decrease of Vd and $T\frac{1}{2}$, though these might simply be explained by the long continual treatment. Previous data showing no difference in patients after 22 days treatment [13], have to be taken into account to describe the slow induction which appears fully after more than 6 months of treatment.

After a prolonged continual treatment with Cy there is a greater decrease in the Vd than in the $T\frac{1}{2}$. This might simply be a reflection of the shortened half life, though other factors may be involved such as vascular modification following regression of some tumoral mass, or modification of the extracellular volume because of reduced abdominal effusion.

The shorter half life is probably due to Cy having an inducing effect on enzymes which transform the drug. The faster metabolism of the compound should increase the peak level of metabolites, but also their rate of disappearance from plasma [16]. We do not yet know whether the peak level or the half life of Cy metabolites is more important for antitumoral activity.

In addition, to be able to discuss the clinical relevance of this data we should know the levels of the single metabolites; there are some active metabolites, namely hydroxyphosphamide, aldophosphamide, and particularly phosphoramide mustard, and some inactive ones such as carboxyphosphamide and ketophosphamide [17, 18].

The problem is clearly very complicated and for the moment we can only conclude that some changes occur in the plasma kinetics of Cy after protracted treatment. Further work is required to ascertain whether modifications to the metabolism of the drug change the concentrations of the active metabolites and consequently affect the antitumoral activity.

Another point to be investigated is the inducing capacity of Cy on microsomal enzymes, since modification of enzymatic activity could influence not only the metabolism of Cy itself but also the metabolism of other drugs given in combination.

This point needs to be investigated as polychemotherapy protocols are being employed more and more widely in clinical cancer treatment.

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