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High-dose melphalan dosage adjustment: possibility of using a test-dose

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Summary. Previous pharmacokinetic studies of i.v. high-dose melphalan (HDM) have demonstrated large interindividual variations in the pharmacokinetic parameters. We therefore studied the possibility of using a test dose of the drug to determine the level of a subsequent therapeutic dose. This study was undertaken to establish whether the pharmacokinetics of melphalan were linear and reproducible within the same patient and determine whether a linear extrapolation could be carried out from the test dose. The first eight patients were studied on two occasions separated by 2 hours (repeatability stage). Although reasonable evidence for linear pharmacokinetics was obtained from these patients, the data suggested a number of factors that might have introduced errors. Therefore, the second group of ten patients were treated on a slightly different protocol on two occasions 24 h apart (linearity stage). The ratios of the two doses ranged from 1 to 8 (repeatability stage) and from 2.6 to 10 (linearity stage). During both stages there was a good correlation between the AUC measured for the second infusion and that predicted from the first ($r = 0.929$ and $r = 0.943$, respectively). We conclude that a test dose can be used to determine the subsequent dose of melphalan necessary to produce a desired AUC.

Introduction

The alkylating agent melphalan has been in use for 30 years in a variety of malignant tumors. A dose-response relationship for melphalan in the treatment of solid tumors was demonstrated in the original work of McElwain et al. [12]. Furthermore, these authors could overcome the myelotoxicity arising from high-dose melphalan (HDM) by combining chemotherapy with autologous bone marrow grafting (ABMG).

In a previous study, we determined the pharmacokinetic parameters of melphalan in 33 patients (18 children, 15 adults) with advanced, malignant, solid tumors [1, 17]. Rapid 5-min infusions of 140 mg/m^2 were given under standard hyperhydration conditions, followed by ABMG 1 day later. Wide interindividual variations in the plasma drug concentrations were observed, the half-lives ranging in the whole group from 18 to 71 min and the AUCs ranging from 175 to 682 mg·l^{-1}·min. Therefore, variability in the efficacy and toxicity of melphalan therapy may be explained in part by the large differences in melphalan elimination kinetics between patients. Therefore, to optimize melphalan therapy in any patient, we studied the possibility of dose individualization based on AUC estimations, using the well-known test-dose method [3, 10].

The present study was carried out in two stages: a repeatability stage in eight patients (2-h interval between doses), followed by a linearity stage in ten other patients (24-h interval between doses). Some of the results arising from the first stage led to slight modifications of our protocol in the second stage.

Patients and methods

Patients. All patients were entered in a phase-II or -III high-dose therapy program at the Centre Léon Bérard. Their main characteristics are presented in Tables 1a (repeatability stage) and 1b (linearity stage). In cases of polychemotherapy, HDM was the last drug given. The parents of juvenile patients were informed of the scientific goal and gave their informed oral consent. Each adult patient gave informed consent to the study.

Eight patients (three children and five adults) were studied during the repeatability stage and ten (two children and eight adults), during the linearity stage. Only 1 linearity-stage patient received 80 mg/m^2 melphalan; all other patients received 140 mg/m^2. The drug was given in two doses (D_1 and D_2), the ratio ranging from 1:1 to 1:10, with a 2-h interval between doses for the repeatability stage and a 24-h interval for the linearity stage.

The drug (Alkeran, Wellcome Laboratories) was reconstituted in the supplied solvent and given i.v. as a 5-min infusion. All patients were on a hyperhydration regimen, as previously described by Ardiet et al. [1]. Frusemide was given only during the repeatability stage. Bone marrow rescue was given to all patients at least 24 h after the second dose of melphalan. One patient (GUI...) received a red blood cell transfusion during the first dose. All blood samples were taken through a silicone Broviac catheter that had previously been introduced into the superior vena cava of each patient via the subclavian vein. As previously described by Lott and Hayton [11], renal function for all patients was assessed from serum creatinine levels; during the linearity stage these levels were determined prior to each melphalan dose on days 1 and 2.

The results of the repeatability study (first eight patients) suggested that the close interval between doses, con-

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Table 1. (a) Patient characteristics, repeatability stage

Name	Sex	Age	Body weight (kg)	Doses[a]		Treatment[b]	Diagnosis[c]	Creatinine clearance (ml/min per 1.73 m²)
				D_1 (mg)	D_2 (mg)			
BER ...	M	25	63	50	200	V-TBI-M	Ewing's sarcoma	120
CIT ...	M	37	63	40	200	BEAM	NHML	100
DAL ...	M	5	17	30	75	BEAM	Burkitt's lymphoma	227
HAR ...	M	16	24	50	100	BEAM	NHML	133
LAZ ...	F	4	18	30	70	V-TBI-M	Sympathoblastoma	236
NOU ...	F	29	55	25	200	VP16-M	Ovarian carcinoma	55
ORL ...	M	13	30	100	100	BEAM	Burkitt's lymphoma	231
SAE ...	F	41	85	50	200	M	Ovarian carcinoma	151

[a] D_1 and D_2, respectively, are the doses given at time 0 and 2 h thereafter
[b] M, melphalan; V, vincristine; TBI, Total-body irradiation; BEAM combination of BCNU, VP16, cytosine arabinoside, and melphalan
[c] NHML, non-Hodgkin's malignant lymphoma

(b) Patient characteristics, linearity stage

Name	Sex	Age	Body weight (kg)	Doses[a]		Treatment[b]	Diagnosis[c]	Creatinine clearance (ml/min per 1.73 m²)	
				D_1 (mg)	D_2 (mg)			day 1	day 2
ALB ...	F	43	53	20	200	BEAM	NHML	95	96
ALI ...	M	25	70	70	180	V-TBI-M	Soft-tissue sarcoma	183	130
BON .. D	F	53	53	30	180	BEAM	NHML	83	61
CER ...	M	19	65	40	230	V-M	Glioblastoma	130	127
COR ...	F	8	20	25	90	V-TBI-M	Rhabdomyosarcoma	94	93
DEC ...	M	39	100	40	120	M	Melanoma	–	188
DUR .. D	M	29	76	40	240	BEAM	NHML	129	111
GUI ...	M	64	60	50	200	BEAM	NHML	76	71
RED ...	M	8	17	15	85	BEAM	Burkitt's lymphoma	209	130
SCA ...	M	21	64	60	200	V-TBI-M	Rhabdomyosarcoma	114	104

[a] D_1 and D_2, respectively, are the doses given at time 0 and 24 h thereafter
[b] M, melphalan; V, vincristine; TBI, Total-body irradiation; BEAM combination of BCNU, VP16, cytosine arabinoside, and melphalan
[c] NHML, non-Hodgkin's malignant lymphoma

comitant use of frusemide, and variations in the duration of the melphalan infusions may have adversely affected the reproducibility and linearity of the data obtained. Therefore, the second (linearity) study was conducted with a 24-h interval between doses and consistent use of frusemide; in addition, both of the melphalan infusions and the subsequent blood samples were carried out by the same nurse.

Blood sampling. All blood samples (3–5 ml) for the pharmacokinetic study were drawn into cooled, heparinized glass tubes (heparinate lithium, Vacutainer). After a reference blood sample had been taken, melphalan was given, with time 0 representing the end of drug infusion. For the repeatability stage, sampling times were 5, 10, 20, 45, 60, and 90 min after the first dose and just before the second, followed by 5, 10, 20, 45, 60, 90, 120, and 180 min after the second infusion. For the linearity stage, samples were taken 5, 10, 15, 30, 45, 60, 90, 120, and 180 min after each infusion. The samples were immediately placed in an ice bath. Blood was centrifuged at 2000 *g* at 0–4° C for 5 min in a refrigerated centrifuge. Plasma was immediately stored at −25° C pending the estimation of melphalan levels; melphalan was assayed according to a procedure previously described elsewhere [1].

Data analysis. Plasma concentrations of melphalan vs time were plotted on a semilogarithmic model. All curves obtained for drug decay were best fitted a biexponential function; using the fitted model, all pharmacokinetic parameters were calculated by the PHARM program [7] with an IBM AT2 system.

To evaluate the possibility of dose adjustment based on a test dose, we undertook the following procedures:
1. Estimation of pharmacokinetic parameters (P_1) after a low-dose melphalan infusion (D_1 mg)
2. Extrapolation to high-dose melphalan (D_2 mg), giving predicted parameters (P_{pred}) and assuming linearity
3. Estimation of pharmacokinetic parameters (P_2) after a high-dose melphalan infusion
4. Comparison of P_{pred} and P_2.

Results

Repeatability stage

The plasma decay curves of two patients are shown in Figs. 1a and 1b. In one patient (LAZ...) (Fig. 1a), who received frusemide only before the first melphalan dose, the elimination half-life was shorter after the first infusion (30.5 min) than after the second (40.7 min). In another patient (NOU...) (Fig. 1b), who received frusemide before each of the two melphalan infusions, the two elimination half-lives were practically identical (43.7 and 41.0 min).

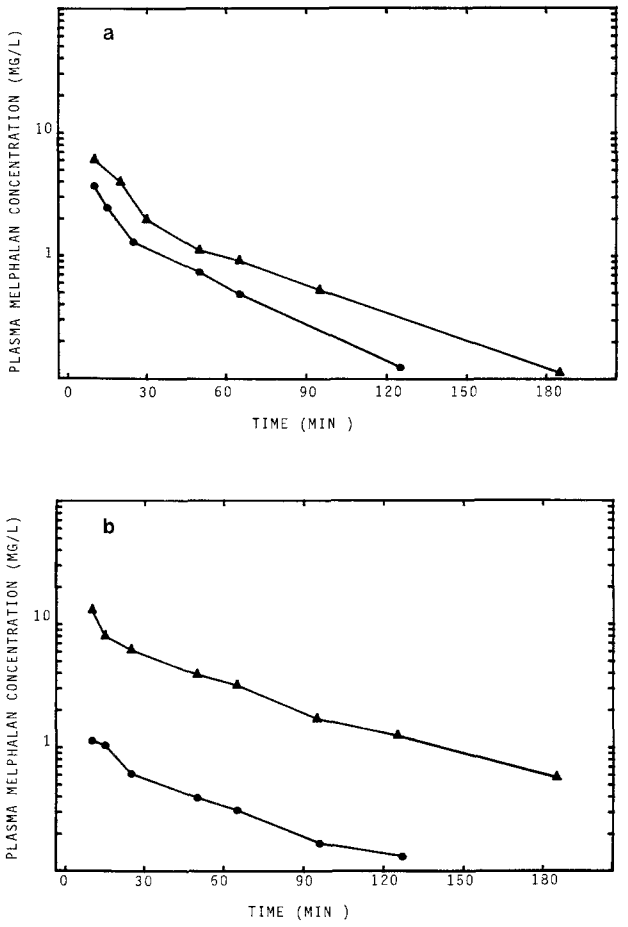

Fig. 1. (a) Melphalan plasma kinetics in patient LAZ..., who received two 5-min infusions with a 2-h dosing interval. Frusemide was given only before the first melphalan infusion (●: first infusion, D_1 = 30 mg, $t_{\beta 1}$ = 30.5 min; ▲: second infusion, D_2 = 70 mg, $t_{\beta 2}$ = 40.7 min). **(b)** Melphalan plasma kinetics in patient NOU..., who received two 5-min infusions with a 2-h dosing interval. Frusemide was given before each melphalan infusion (●: first infusion, D_1 = 25 mg, $t_{\beta 1}$ = 43.7 min; ▲: second infusion, D_2 = 200 mg, $t_{\beta 2}$ = 41.0 min)

The pharmacokinetic parameters of the eight patients studied in this stage are presented in Table 2. Large differences were observed between the two melphalan infusions for the distribution half-life (t_α) and the extrapolated value of drug concentration at time 0 during the first and the second phases (C_α and C_β, respectively). In contrast, the elimination half-life (t_β), volume of distribution at steady state (V_{dss}), and clearance (Cl) were similar. From the relative error values, there were apparently no major differences between the main parameters (t_β, V_{dss}, and Cl) estimated from the second melphalan infusion (P_2) and those predicted (P_{pred}) from the first infusion. Furthermore, the AUC_2 and the AUC predicted (AUC_{pred}) from AUC_1 were well correlated (r = 0.929; AUC_{pred} = 0.794 AUC_2 +63.94). The ratios of these parameters are presented in Table 3, where the elimination half-life ratios range from 0.89 to 1.42, and AUC ratios are close to the dose ratios.

Linearity stage

The pharmacokinetic parameters are presented in Table 4. Considerable variation in the values t_α, C_α, and C_β was observed between the two doses. In contrast, consideration of the values t_β, AUC, V_{dss}, and Cl supports the hypothesis of linearity, as evidenced by the relative error values (Table 4) and the ratios of these parameters between the two drug infusions (Table 5). As in the repeatability stage, the AUC_{pred} and AUC_2 were well correlated (r = 0.943; AUC_{pred} = 1.02 AUC_2 +0.05): the representation of AUC_{pred} versus AUC_2 (Fig. 2) shows a good data distribution around the line $y = x$.

The last point investigated was the accuracy of the melphalan dose measurement. Although it was easy to measure doses ranging from 85 to >200 mg (for the second infusion) in 100-mg drug flasks, accuracy was more difficult for doses as small as 15 mg (for the first infusion). Hence, we compared the first dose (D_1) of melphalan with its value estimated (D_{1e}) from the second-dose kinetics data. The results (Table 6) show good dosing accuracy.

Discussion

In recent years, various methods have been proposed to individualize drug dose for each patient, involving statistical correlations between physiological (e.g., age, body weight, sex) or biological parameters (e.g., renal function) that evidence patient physiopathology and pharmacokinetic parameters that indicate drug behavior under therapeutic conditions. When such correlations occurred, the dose regimen could be predicted using nomograms [2, 14, 15] or computer programs, exemplified by the methods used for the individualization of gentamicin dose in patients with renal insufficiency [4, 6, 16]. Other prediction methods have been developed, such as that for the individualization of phenytoin [8, 18] or aminophylline dose in patients with respiratory insufficiency [5, 9, 13]. Unfortunately, such correlations are infrequently established.

Few data have been reported in the literature as to the optimization of anticancer drug therapy by using pharmacokinetic data for each patient. Such a method was used for predicting high-dose methotrexate infusions [10], but it has never previously been used for melphalan.

In a previous study by Tranchand [17], no correlation was found between pretreatment organ function and pharmacokinetic parameters. Therefore, we studied the possibility of individualizing melphalan dosing by a pharmacokinetic characterization of each patient. Tables 2 and 4 indicate that for the first and second doses of melphalan, the main parameters t_β, AUC extrapolated to 140 mg/m^2, Cl, and V_{dss} were in good accordance with values obtained previously [17]: t_β = 44.5±16.2 min, AUC = 423±147 mg·l^{-1}·min, Cl = 0.438±0.178 l·min^{-1}·m^{-2}, and V_{dss} = 14.6±5.1 l/m^2. Thus, it appears that melphalan pharmacokinetics are not dose-dependent.

During the repeatability stage, slight differences in the three main pharmacokinetic parameters t_β, AUC, and Cl occurred between the values estimated from the second drug infusion (P_2) and those predicted (P_{pred}) from the first dose. The discrepancies observed could be related to the fact that some patients received frusemide only before the first melphalan infusion. The duration of frusemide's pharmacological effect is about 2 h; thus, the influence of this drug could explain the t_β differences observed between the two melphalan doses (Figs. 1 a, b). Another explanation could involve some irregularity in melphalan infusion

Table 2. Melphalan pharmacokinetic parameters in the repeatability-stage group after the two drug infusions (1 and 2)

Name	D_2/D_1[a]	t_α		t_β[b]			C_α		C_β	
		1 (min)	2 (min)	1 (min)	2 (min)	%	1 (mg/l)	2 (mg/l)	1 (mg/l)	2 (mg/l)
BER ...	4	4.8	8.5	38.2	41.7	9.3	3.5	7.9	1.1	2.2
CIT ...	5	6.7	5.4	43.9	44.4	1.0	2.1	23.8	0.5	2.4
DAL ...	2.5	7.7	5.5	36.9	32.7	−11.4	6.2	11.7	1.3	5.3
HAR ...	2	1.6	17.8	30.6	43.5	42.5	19.9	4.1	2.0	2.9
LAZ ...	2.3	3.8	4.4	30.4	40.7	34.1	7.6	28.0	2.1	2.6
NOU ...	8	2.9	1.8	43.7	41.0	−6.0	6.4	77.1	0.8	9.0
ORL ...	1	6.5	4.5	30.5	27.1	−11.2	7.1	11.2	2.6	3.9
SAE ...	4	3.8	4.8	45.5	48.7	7.1	8.0	25.8	1.0	3.3

	AUC[b]			V_{dss}[b]			Cl[b]		
	1 (mg·l^{-1}·min)	2 (mg·l^{-1}·min)	%	1 (l·m^{-2})	2 (l·m^{-2})	%	1 (l·min^{-1}·m^{-2})	2 (l·min^{-1}·m^{-2})	%
BER ...	82	231	−31.6	14.0	19.5	39.0	0.446	0.531	19.1
CIT ...	53	339	26.1	18.8	11.5	−38.5	0.477	0.414	−13.2
DAL ...	138	341	−3.2	9.3	10.7	14.9	0.328	0.325	−0.9
HAR ...	134	286	4.5	10.5	16.0	51.5	0.490	0.347	−29.2
LAZ ...	133	327	3.6	10.0	9.1	−9.4	0.377	0.461	22.3
NOU ...	79	732	14.6	8.4	7.4	−12.2	0.269	0.217	17.8
ORL ...	178	224	21.7	12.2	9.0	−26.7	0.510	0.348	−31.8
SAE ...	111	412	−9.7	10.6	11.7	10.3	0.221	0.305	38.0

[a] D_2/D_1, ratio of melphalan doses given
[b] %, Relative difference in parameters between the two drug infusions

Table 3. Parametric ratios between the kinetics of the two successive infusions in the repeatability-stage group

Name	D_2/D_1	$t_{\beta 2}/t_{\beta 1}$	AUC_2/AUC_1	Cl_2/Cl_1	V_{dss2}/V_{dss1}	$\frac{AUC_2}{AUC_1} \cdot \frac{D_1}{D_2}$
BER ...	4	1.09	2.74	1.19	1.39	0.69
CIT ...	5	1.01	6.30	0.87	0.61	1.26
DAL ...	2.5	0.89	2.42	0.99	1.15	0.97
HAR ...	2	1.42	2.09	0.71	1.52	1.05
LAZ ...	2.3	1.30	2.41	1.22	0.91	1.05
NOU ...	8	0.94	9.17	0.81	0.88	1.15
ORL ...	1	1.13	1.22	0.68	0.74	1.22
SAE ...	4	1.07	3.61	1.38	1.10	0.90

(since it was done manually with a syringe), evidenced by the large differences in t_α and C_α extrapolated to D_2 observed between the two doses (Table 2).

Nevertheless, if we consider parametric ratios between the kinetics of the two successive melphalan infusions (Table 3), we can see that, in spite of the frusemide administration and manual infusions, the pharmacokinetics appear linear after an i.v. infusion; indeed, t_β, Cl, and V_{dss} ratios were close to 1 and AUC ratios were close to the dose ratios.

In an attempt to minimize the differences observed during the repeatability study, two changes were made in the linearity study: frusemide was suppressed in the therapeutic protocol, and the two melphalan infusions and subsequent blood samples were carried out in all patients by the same nurse.

If we take into account that the mean elimination half-life (t_β) of melphalan was 44 ± 16 min [17], a 24-h interval between the two drug infusions is sufficient for a linearity study. Furthermore, since patients did not receive any treatment between the test dose and therapeutic dose, their pharmacokinetics could not have been modified by another chemotherapeutic agent.

In all patients, except one (GUI ...) who received a red blood cell transfusion during the first melphalan infusion, we observed discrepancies mainly in t_α and C_α (evidencing irregular infusion by syringe) but not in t_β, AUC, V_{dss}, and Cl, which are less dependent on variations in drug delivery and are better suited for establishing linearity (Table 4). Furthermore, Table 4 shows that in all cases but one (GUI ...) the relative differences between the AUC_{pred} and AUC_2 were always $< 15\%$. This result is important assuming that AUC is the most significant factor in determining toxicity and therapeutic effect.

Correlations between the AUC_{pred} and AUC_2, calculated during the two separate parts of the present study

Table 4. Melphalan pharmacokinetic parameters in the linearity-stage group after the two drug infusions

Name	D_2/D_1[a]	t_α		t_β[b]			C_α		C_β	
		1 (min)	2 (min)	1 (min)	2 (min)	%	1 (mg/l)	2 (mg/l)	1 (mg/l)	2 (mg/l)
ALB ...	10	5.0	4.7	39.2	37.1	−5.4	2.5	35.5	0.8	8.5
ALI ...	2.6	5.9	3.8	45.4	39.0	−14.1	5.2	19.5	0.8	2.9
BON .. D	6	7.8	7.9	49.2	48.1	−2.1	1.4	9.2	0.6	3.2
CER ...	5.8	7.6	5.1	55.2	47.6	−13.7	2.0	14.5	0.7	3.9
COR ...	3.6	6.4	15.2	66.7	66.0	−1.1	3.9	7.4	1.4	4.6
DEC ...	3	11.6	6.2	87.3	56.5	−35.3	0.9	5.6	0.2	0.7
DUR .. D	6	2.9	6.2	31.4	42.4	35.0	6.7	14.4	0.8	3.4
GUI ...	4	9.4	13.6	42.5	48.2	13.6	0.6	4.3	0.7	3.6
RED ...	5.7	6.1	9.0	55.0	51.1	−7.1	2.2	10.1	0.5	3.5
SCA ...	3.3	6.3	7.3	50.2	52.7	4.9	1.6	9.6	1.5	4.2

	AUC[b]			V_{dss}[b]			Cl[b]		
	1 ($mg \cdot l^{-1} \cdot min$)	2 ($mg \cdot l^{-1} \cdot min$)	%	1 ($l \cdot m^{-2}$)	2 ($l \cdot m^{-2}$)	%	1 ($l \cdot min^{-1} \cdot m^{-2}$)	2 ($l \cdot min^{-1} \cdot m^{-2}$)	%
ALB ...	62	691	11.5	8.7	6.9	−21.0	0.237	0.226	−4.6
ALI ...	95	266	8.9	16.1	13.6	−15.6	0.578	0.461	−20.2
BON .. D	57	326	−4.7	10.0	18.7	−1.9	0.377	0.399	5.8
CER ...	73	373	−11.1	16.8	16.3	−2.5	0.305	0.357	17.0
COR ...	165	598	0.7	14.3	13.8	−3.6	0.197	0.191	−3.0
DEC ...	39	109	−6.8	42.2	26.7	−36.8	0.560	0.649	15.9
DUR .. D	65	334	−14.4	8.6	14.8	72.7	0.427	0.418	−2.1
GUI ...	49	331	68.9	30.6	19.3	−35.8	0.599	0.353	−41.1
RED ...	61	389	12.5	19.7	16.3	−17.3	0.384	0.329	−14.3
SCA ...	122	417	2.6	17.2	15.5	−9.9	0.279	0.279	0.0

[a] D_2/D_1, ratio of melphalan doses given
[b] %, Relative difference in parameters between the two drug infusions

Table 5. Parametric ratios between the kinetics of the two successive infusions in the linearity-stage group

Name	D_2/D_1	$t_{\beta 2}/t_{\beta 1}$	AUC_2/AUC_1	Cl_2/Cl_1	V_{dss2}/V_{dss1}	$\frac{AUC_2}{AUC_1} \cdot \frac{D_1}{D_2}$
ALB ...	10	0.95	11.15	0.95	0.79	1.11
ALI ...	2.6	0.86	2.80	0.80	0.84	1.08
BON .. D	6	0.98	5.72	1.06	0.98	0.95
CER ...	5.8	0.86	5.11	1.17	0.97	0.88
COR ...	3.6	0.99	3.62	0.97	0.96	1.01
DEC ...	3	0.65	2.79	1.16	0.63	0.93
DUR .. D	6	1.35	5.14	0.98	1.73	0.86
GUI ...	4	1.14	6.76	0.59	0.60	1.69
RED ...	5.7	0.93	6.38	0.86	0.83	1.12
SCA ...	3.3	1.05	3.42	1.00	0.90	1.04

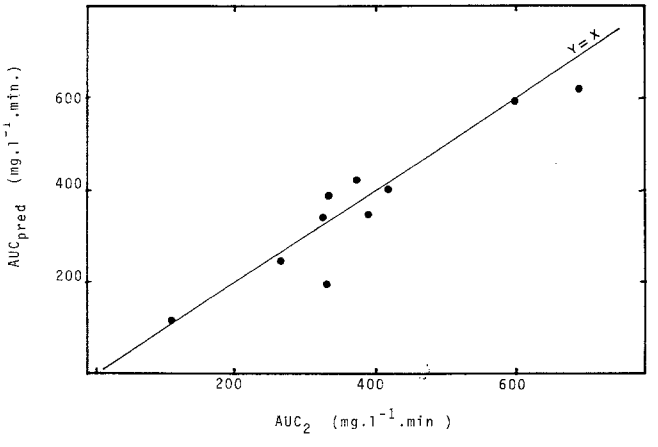

Fig. 2. AUC predicted (AUC_{pred}) from the first-infusion kinetics vs the AUC estimated from the second-infusion kinetics (AUC_2) during the linearity stage

Table 6. Comparison between first dose of melphalan (D_1) and its value estimated (D_{1e}) from the second-dose kinetics data

Name	D_1 (mg)	D_{1e}[a] (mg)	$\lvert D_1 - D_{1e} \rvert$ (mg)
ALB ...	20	18	2
ALI ...	70	64	6
BON .. D	30	31	1
CER ...	40	45	5
COR ...	25	25	0
DEC ...	40	43	3
DUR .. D	40	47	7
GUI ...	50	–	–
RED ...	15	13	2
SCA ...	60	59	1

[a] $D_{1e} = D_2 \cdot AUC_1/AUC_2$

(repeatability stage: $r = 0.929$ and $AUC_{pred} = 0.794\ AUC_2 + 63.94$; linearity stage: $r = 0.943$ and $AUC_{pred} = 1.02\ AUC_2 + 0.05$), indicate that the results of the linearity study were close to the values predicted by presuming linear kinetics. In our opinion, this reflects the slight modifications in the protocol for the latter part of the study, especially the test-dose measurement. In addition, the patient whose V_{dss} value was larger after the first infusion than after the second had received a red blood cell transfusion during the first dose, which could have caused this discrepancy.

In one patient from the repeatability-stage group (NOU ...) presenting moderate or high creatinine levels, it is interesting that the half-life elimination (41.03 min) was close to the mean half-life previously obtained elsewhere [17]. Moreover, the two patients from the linearity-stage group (ALI ... and RED ...) who had wide variations in serum creatinine from day 1 to day 2 had similar pharmacokinetic parameters after the two melphalan infusions, and their P_{pred} values were close to their P_2 values. These results support previous observations that renal function does not significantly alter melphalan pharmacokinetics [17] and is not an impediment to dose individualization using the test dose.

The results of the present study are well suited for establishing the linearity of melphalan pharmacokinetics, dose ratios ranging from 1 to 10. At the present time, we can individualize melphalan dosing by pharmacokinetic characterization of each patient using the AUC after the test-dose administration (with particular emphasis on the accuracy of the test-dose measurement). We believe this to be important but such a dose adjustment may be routinely used only after the AUC reference value has been determined. The AUC-toxicity relationship should provide a target value for the maximization of the AUC for each patient, with acceptable toxicity.

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