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Acknowledgements—This work was suported in part by Institut Gustave-Roussy grant 84 D 19 and Electricité de France grant. We are indebted to Mrs Andrée Dutreix, Dr Hélène Sancho Garnier and Pr Maurice Tubiana for their assistance and useful comments. We are grateful to Mrs Marie-Thérèse Praquin for her technical assistance in collecting data and Mrs V. Kamenopoulos for assistance in dose recalculation. We thank Mrs Brigitte Dupont for typing this manuscript, and Mrs Lorna Saint Ange for assistance in its preparation.

Eur J Cancer, Vol. 27, No. 10, pp. 1222–1226, 1991.
Printed in Great Britain

0277–5379/91 $3.00 + 0.00

Phase I Study of Vintriptol, a Tryptophan Ester of Vinblastine

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Vintriptol, a tryptophan ester of vinblastine, is a new vinca alkaloid derivative. Preclinical studies have demonstrated its antitumour activity in a large variety of animal models. In this phase I study, 47 patients with advanced cancer were exposed to escalating doses of vintriptol, starting at 6 mg/m² and following a modified Fibonacci schedule. The drug was administered as an intravenous push on a weekly schedule. Myelosuppression was the dose-limiting toxicity and the maximum tolerated dose was 45 mg/m². Other toxicities consisted of mild nausea and vomiting and the occurrence of fever and dryness of the mouth immediately after drug administration. Neurotoxicity, a major side-effect of other vinca alkaloids, was insignificant. 1 partial remission in a patient suffering from colorectal cancer and 1 minor response in a patient with a metastatic tumour of the cutaneous appendagous glands were documented. Pharmacokinetics of vintriptol were evaluated at the highest dose levels. A dose schedule of 40 mg/m² vintriptol per week is recommended for phase II studies.
Eur J Cancer, Vol. 27, No. 10, pp. 1222–1226, 1991.

INTRODUCTION

VINCA ALKALOIDS rank among the main groups of anticancer agents because of their broad spectrum of activity and their unique mechanism of action. Vintriptol N-(deacetyl-0-4-vinblastinoyl-23)-L-ethyl tryptophanate methane sulphonate was synthesised in order to increase the therapeutic ratio of vinca alkaloids by diminishing myelosuppression and neurotoxicity. It is the ethyl ester of L-tryptophan and the sulphate of an alkaloid, vincaleukoblastine or vinblastine.

Vintriptol (MW base 969) is obtained by preparation of a monohydrazide of vinblastine, the formation of an acid and then the coupling of the tryptophan ethyl ester at the C23 position.

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Revised and accepted 23 May 1991.

Preclinical studies [1–3] have demonstrated that the overall toxicity of the compound is at least five times less than vinblastine. When compared at optimal doses, vintriptol was at least as effective as vinblastine against murine tumours such as F388 and L1210 leukaemias, B16 melanoma, Lewis lung carcinoma and C26 colon carcinoma.

In a phase I study, Ceulemans *et al.* [4] treated 20 patients with advanced cancer with doses ranging from 2.5 mg/m² to 30 mg/m². Main side-effects were dryness of the mouth occurring immediately after administration of the drug and myelosuppression. Leucopenia seemed to be the dose-limiting factor, emerging at a dose of 20 mg/m². At 30 mg/m², the maximum dose reached, white blood count values lower than 2×10^9/l were not observed. Neurotoxicity was insignificant. 2 cases of disease stabilisation were observed in patients with non-small cell lung cancer.

In this study, the maximum tolerated dose (MTD) had not been reached and we therefore performed a further phase I study to determine this.

Table 1. Patients' characteristics

Total number	47
Male/female	33/14
Age	Median 57, range 20–76
Primary tumours	
Colorectal	14
Gastric	2
Soft tissue	6
Lung	5
Renal cell	4
Urogenital	4
Breast	3
Melanoma	2
Cervical	1
Ovary	1
Non-Hodgkin lymphoma	1
Multiple myeloma	1
Adnex tumour of skin	1
Primary unknown	2
Previous treatment	
Chemotherapy only	23
Radiotherapy only	6
Radiotherapy and chemotherapy	18
No prior treatment	0
Performance status (WHO)	Median 1, range 0–3

PATIENTS AND METHODS

Patients' characteristics are shown in Table 1. 47 patients, 33 men and 14 women, ranging in age from 20 to 76 years, were entered in this study. All patients had pathological confirmation of cancer and all had been heavily pretreated with chemotherapy and/or radiotherapy. Patients had recovered from all toxic effects from prior treatments and were at least 4 weeks beyond any prior chemotherapy or radiotherapy. All patients had a minimum life expectancy of 6 weeks and the median performance status (WHO) was 1 with a range of 0 to 3. The patients had evidence of adequate bone marrow function (WBC counts $> 4 \times 10^9$/l and platelet counts $> 100 \times 10^9$/l), adequate liver function (serum bilirubin < 1.5 mg/100 ml), and adequate renal function (serum creatinine < 100 mol/l).

Prior to beginning therapy, each patient underwent an evaluation including history and physical examination, tumour measurements, chest X-ray, electrocardiogram (ECG) and neurological examination. Pretreatment evaluation also included complete blood cell counts and serum chemistries. These parameters were followed weekly while the patient was on study.

Table 2. Non-haematological toxicity (WHO)

Dose (mg/m²)	n	No. of courses	Fever						Nausea and vomiting					
			0	1	2	3	4	NE	0	1	2	3	4	NE
6	1	3	2		1				2		1			
12	2	12	9	2	1				12					
16	3	15	13	1	1				12	3				
20	3	21	20	1					8	8	5			
26	3	24	19	3	2				20	1	3			
34	12	51	44	4	3				24	13	4			
40	8	37	26	5	6				18	13	5	1		
45	15	47	10	16	15			6	16	18	8	1		4

NE = not evaluable.

Table 3. Haematological toxicity

Dose (mg/m²)	n	No. of courses	WBC ($\times 10^9$/l) Median nadir	Range	Median day	Range
6	1	3	6.7	5.3– 7.4	8	
12	2	12	7.4	5.5–14.3	8	2–15
16	3	15	5.4	3.2– 8.5	8	7–16
20	3	21	4.6	3.6–16.9	8	7–16
26	3	24	5.5	3.6– 8.3	8	8–15
34	12	51	4.0	0.8–16.8	8	3–15
40	8	37	3.0	0.6–14.3	6	3–15
45	15	47	3.3	0.7–10.7	7	2–15

Patients were treated with vintriptol in escalating doses following a modified Fibonacci escalation schedule. Dose steps were 6, 12, 16, 20, 26, 34, 40 and 45 mg/m² in, respectively, 1, 2, 3, 3, 12, 9 and 14 patients. Patients were scheduled to be treated on a weekly basis by intravenous push (5 min) injections with vintriptol. Those who showed objective tumour response, or, in the case of non-evaluable disease, subjective improvement with no sign of disease progression, continued treatment for as long as improvement lasted.

Pharmacokinetic studies were performed in 10 patients at the highest dose levels during the first course of the treatment. Blood samples were drawn and collected in heparinised tubes before administration and 1, 5, 10, 15, 30, 45 min and 1, 1.5, 2, 3, 4, 6, 12, 18, 24 and 48 h postinfusion. Plasma was separated immediately by centrifugation (10 min, 2000 *g*) and kept at −20°C until analysis. Analyses were performed within 2 months. Determination of the vintriptol concentration was performed by high performance liquid chromatography [5]. The sample pretreatment involved liquid–liquid extraction of the buffered (pH=3) sample with chloroform. Vinblastine was used as an internal standard. Separation of the analytes was achieved on a Hypersil ODS (5 m) column. The mobile phase was composed of acetonitril in a phosphate buffer pH 6.0. The flow rate was 0.4 ml/min. Detection was carried out electrochemically at +0.70 Volts. The limit of detection was 2 g/l. Standard samples were prepared by making the appropriate dilutions of vintriptol in blank plasma. These samples were analysed with each run for preparation of a calibration curve. Control samples were analysed with each series of samples to determine the day to day accuracy. Patient and control samples were analysed in duplicate and accuracy within a day was calculated from these duplicates. Standard and control samples were stored at −20°C. Peak height ratios of vintriptol/vinblastine were used for the calculations of concentrations. A three-compartment model was used to fit the plasma concentration-time curves [5].

RESULTS

47 patients were entered in this study. 1 patient, entered at the 40 mg/m² dose level, decided to stop treatment following the first course and could not be considered evaluable. 1 of the remaining 46 patients started at the 6 mg/m² dose level (three courses) and continued at the 12 mg/m² dose level.

Toxicity

Non-haematological toxicity. Dry mouth was observed occasionally, but did not seem to be related to dose. Fever was

Table 4. Haematological toxicity: WBC (WHO)

Dose (mg/m²)	*n*	No. of courses	0	1	2	3	4	NE
6	1	3	3					
12	2	12	12					
16	3	15	11	4				
20	3	21	17	3				1
26	3	24	21	3				
34	12	51	26	8	10	4	2	1
40	8	37	16	3	13	4	1	
45	15	47	17	9	8	11	1	1

Table 5. Haematological toxicity: platelets (×10⁹/l)

Dose (mg/m²)	*n*	No. of courses	Median nadir	Range	Median day	Range
6	1	3	283	275–290	8	
12	2	12	263	120–325	8	2–23
16	3	15	235	175–440	8	7–8
20	3	21	267	130–568	8	7–16
26	3	24	203	155–495	8	8–15
34	12	51	248	65–538	8	2–21
40	8	37	125	24–324	4	2–8
45	15	47	165	41–390	5	3–18

consistently observed. Even at the lowest escalation step of 6 mg/m², fever grade 2 (WHO) was observed and seemed to be more frequent with higher dosages. Details of fever according to WHO grading are given in Table 2.

At the highest dose level of 45 mg/m², fever of longer duration and of increasing severity was noted in a substantial number of patients. Nausea and vomiting scored only grade 2 in the majority of the observed incidences, but seemed to occur more frequently as dose levels were increased (see Table 2). Neurotoxicity was not reported more than occasionally, even when patients were treated for a long period. Only in 2 patients treated at 12 and 26 mg/m² did paresthesias occur (WHO grade 1).

Haematological toxicity. Leucocytopenia and thrombocytopenia were considered to be the dose limiting factors. As is shown in Tables 3, 4, 5 and 6 moderate thrombocytopenia and severe leucocytopenia were observed at the 34 mg/m² dose level.

Table 6. Haematological toxicity: platelets (WHO)

Dose (mg/m²)	*n*	No. of courses	0	1	2	3	4	NE
6	1	3	3					
12	2	12	12					
16	3	15	15					
20	3	21	20					1
26	3	24	24					
34	12	51	46	3	1			1
40	8	37	26	4	4	2	1	
45	15	47	38	5	2	1		1

Table 7. Dose reduction/delay

Patient	Initial WBC	Total courses	Dose reduction	Course no.	WBC	Delay (week)	Course no.	WBC
1	22.0	10						
2	10.3	3						
3	9.5	2	50%	2	2.5			
4	8.7	3				1	3	2.1
5	8.3	3	50%	3	2.5			
6	8.1	4						
7	8.1	4				1	3	1.5
8	7.8	4	50%	3	3.4			
9	6.9	3				2	2	2.9
10	4.6	9						
11	4.3	2						
12	3.8	4	50%	2	2.6	2	3	1.3
						3	4	2.3

34 mg/m² in 4 of 12 patients.

However, there was a large interpatient variation in the WBC counts and the platelet counts. Notwithstanding a WBC median nadir of 3.3 × 10⁹/l at 45 mg/m², the minimum values of the range (0.7–10.7) indicate the severe leucocytopenia at this dose level (Table 3). Data are summarised in Table 4 according to the grading system of the WHO which shows that at the 45 mg/m² level, 11 of the 47 courses resulted in a grade 3 haematological toxicity. This seems, notwithstanding 17 out of 47 courses with no haematological toxicity, to be dose-limiting.

Also with respect to thrombocytopenia it was clear that although median values were of no significance some patients did experience severe platelet nadirs (see Table 5).

As a result of severe leucocytopenia and thrombocytopenia which were first observed at a dose of 34 mg/m²—appearing in most cases after the second treatment course—the dose of vintriptol, administered on a weekly schedule had to be modified according to the following guidelines. In the case of a WBC of 2.5–3.5 × 10⁹/l or a platelet count of 50–100 × 10⁹/l, a 50% dose reduction was applied, while in the case of a WBC below

Table 8. Dose reduction/delay

Patient	Initial WBC	Total courses	Dose reduction	Course no.	WBC	Delay (week)	Course no.	WBC
1	51.3	3						
2	18.8	1						
3	17.1	2						
4	9.2	3						
5	8.8	10	50%	6	2.6	1	3	2.9
			50%	7	1.8			
6	7.7	3				1	3	1.5
7	6.2	6	50%	3	2.1			
			75%	4	0.6	1	4	0.6
			75%	5	2.9	1	5	2.9
			75%	6	2.0			
8	5.6	9				2	3	1.9
						2	5	2.2
						2	7	1.6
						2	8	2.4
						2	9	2.0

40 mg/m² in 3 of 5 patients.

Table 9. Dose reduction/delay

Patient	Initial WBC	Total courses	Dose reduction	Delay (week)	Course no.	WBC
1	19.2	2	—			
2	12.6	4	—	1	3	1.5
3	11.9	4	—	1	3	1.5
				2	5	1.6
4	11.1	2	—			
5	10.9	3	—			
6	10.0	3	—			
7	10.0	2	—			
8	9.1	13	—	1	3	1.6
				1	5	1.7
				1	8	1.5
				1	11	2.7
				1	13	2.2
9	8.9	3	—	2	3	1.4
10	8.6	2	—			
11	8.1	2	—			
12	8.1	2	—			
13	6.6	3	—			
14	5.7	1	—			
15	4.5	1	—			

45 mg/m^2.

2.5 × 10^9/l or a platelet count below 50 × 10^9/l, treatment was delayed for 1 week.

At the 34 mg/m^2 dose level, dose modification (4 of the 51 courses) and treatment delay (5 of the 51 courses) were necessary. This was more pronounced at the 40 mg/m^2 dose level; 6 of the 37 courses needed dose modification and 9 of the 37 courses delay of treatment. At the 45 mg/m^2 dose level in 9 of the 47 courses the WBC counts reached such low values that delay of treatment was always necessary.

Whether the reported thrombocytopenia nadir of platelets under 2 and 3 is the result of myelosuppression caused by vintriptol or the result of redistribution of the cells caused by this drug is difficult to ascertain with the available data. Because the treatment was given on a weekly schedule, it is difficult to say whether the reported nadirs on day 2 or 3 of the second treatment course was caused by myelosuppression due to the first course or by redistribution of the cells due to the second vintriptol injection. For the leucocytes this phenomenon was not noticed. Also, in some patients we saw the occurrence of a second nadir of the platelet count; the first nadir appeared on day 2 or 3 of the treatment cycle and was shortly followed by a recovery and the second nadir occurred on days 13–21. These data suggest that, besides myelosuppression of the WBC and the platelets, vintriptol may cause a reversible redistribution of the platelets.

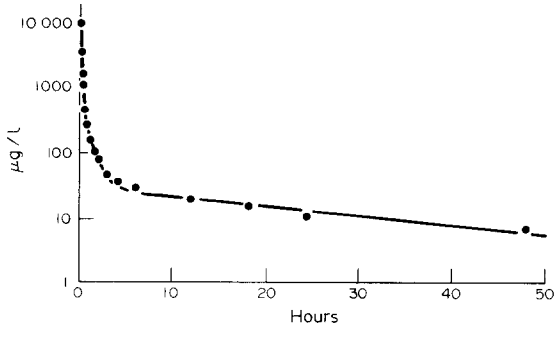

Fig. 1. Plasma concentration decay curve. A patient received 45 mg/m^2 vintriptol as a short intravenous infusion. The concentration in plasma decreased in accordance with a three compartment open model.

Table 10. Vintriptol pharmacokinetic parameters

Patient	Dose (mg)	Body weight (kg)	Plasma half-lives (h) α	β	γ	AUC mg.h/l	V_d (l/kg)	CL (l/h/kg)
1	80*	66	0.0570	0.651	15.0	2.37	11.0	0.511
2	70*	50	0.0656	0.619	20.6	2.22	18.7	0.630
3	75*	65	0.0982	1.394	24.1	3.05	13.1	0.378
4	95*	88	0.0582	1.055	18.3	2.17	13.1	0.497
5	90*	84	0.0611	1.055	21.5	2.80	11.8	0.382
6	85*	81	0.0740	1.010	18.3	3.23	8.6	0.325
Mean*		0.0690	0.964	19.6	2.64	12.7	0.454	
S.D.*		0.0155	0.290	3.1	0.45	3.4	0.113	
7	85†	65	0.0621	1.072	21.2	2.75	14.5	0.476
8	100†	76	0.0338	0.727	24.2	2.32	19.8	0.567

*45 mg/m^2, †50 mg/m^2.
AUC = area under the concentration–time curve, V_d = volume of distribution, CL = clearance.

Therapeutic effects

1 partial remission in a patient suffering from a very slowly progressing inoperable colon cancer and 1 minor response in a patient with a disseminated adnex tumour of the skin were documented.

Pharmacokinetics

A typical concentration versus time curve is depicted in Fig. 1. The results of the pharmacokinetic study are summarised in Table 10. The ranges of the pharmacokinetic parameters are narrow, indicating little interpatient variability. This is in contrast with the results obtained for other vinca alkaloids [6]. The half-lives are comparable to those reported for vinblastine. The slightly lower volume of distribution combined with a 5-fold higher MTD compared to vinblastine results in an approximately 10-fold higher plasma area under the concentration–time curve (AUC).

DISCUSSION

The maximum tolerated dose of vintriptol, given on a weekly schedule, was 45 mg/m^2. Haematological toxicity was the dose-limiting factor and dose modification was frequently necessary and substantial. Further research is necessary to elucidate whether the reported thrombocytopenia is caused by myelosuppression or cell redistribution. The pharmacokinetic parameters for vintriptol showed little interpatient variation. The plasma AUC of vintriptol was about 10-fold higher than that of vinblastine. The recommended dose for further testing should be 40 mg/m^2 given in the weekly administration regimen, one step below the highest dose reached. In particular, the almost complete lack of clinically manifested neurotoxicity warrants further testing of this new vinca alkaloid.

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Eur J Cancer, Vol. 27, No. 10, pp. 1226–1230, 1991.
Printed in Great Britain

0277–5379/91 $3.00 + 0.00

Prognostic Factors in Patients with Liver Metastases from Colorectal Carcinoma Treated with Discontinuous Intra-arterial Hepatic Chemotherapy

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48 patients with colorectal cancer metastatic to the liver were implanted with a subcutaneous access system allowing hepatic intra-arterial perfusion. Regional chemotherapy used 5-fluorouracil, while 17 patients also received low-dose mitomycin at the beginning of the study. Responses to the treatment occurred in 29 patients (60%) and median survival was 14.4 months. Toxicity included gastroduodenal erosions in 12.5% of the patients, leucopenia in 20.8%, catheter thrombosis in 42% and arterial thrombosis in 50%. 2 patients died of digestive haemorrhage probably related to treatment. When individually analysed, four factors were found to significantly affect survival: presence of hepatomegaly (defined as palpable liver edge exceeding the right costal margin by more than 5 cm) ($P = 0.006$), percentage of hepatic replacement superior to 50% ($P = 0.003$), more than four metastases ($P = 0.025$) and hypovascularised metastases at radionuclide liver scan with ^{99m} technetium-labelled macroaggregate albumin (MAA) ($P = 0.04$). The effect of the four variables on the observed survival time was analysed using a Cox regression model. Two variables were found to have simultaneously influenced survival. Presence of hepatomegaly emerged as the more significant ($P = 0.0001$), the other being hypovascularised metastases at ^{99m}Tc-MAA.
Eur J Cancer, Vol. 27, No. 10, pp. 1226–1230, 1991.

INTRODUCTION

HEPATIC METASTASES are the most common cause of death in patients with colorectal carcinoma [1]. For these metastases the therapeutic possibilities vary according to their extension and the context in which they occur.

When hepatic metastases are isolated, the best treatment remains surgical excision with a 20–30% 5-year survival rate [2–4]. Unfortunately, such surgery is only possible in about 10% of cases. When it is impossible, only low-efficacy intravenous chemotherapy with 5-fluorouracil (5-FU) can be envisioned [5, 6]; but for certain patients locoregional treatments may also be considered, among which intra-arterial hepatic chemotherapy (IAHC) is a first-line choice. A number of studies have demonstrated a response rate of 50–70% to intrahepatic administration of 5-FU or 5-fluorodeoxyuridine (FUDR), even in patients previously treated with systemic 5-FU [7–9].

Factors affecting survival in patients with colorectal metastases treated by locoregional therapy have been investigated by few authors. Almersjo *et al.* [10] found that survival time was inversely related to percentage of hepatic replacement (PHR). Fortner *et al.* in a multivariate study [5] found PHR, lymphnode metastases and prior chemotherapy to be the most significant determiners of survival in patients treated by IAHC. In Kemeny's multivariate prognostic study [11], the most important factor affecting survival was the assessment of liver involvement evaluated by radionuclide liver scan and computed tomography (CT). Still, the interdependence of clinical, intra-