Anti-Cancer Drugs, 3, pp. 225 231

Phase I trial of Perrimustine, a new cysteamine (2-chloroethyl) nitrosourea: an intrapatient escalation scheme

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The recently synthesized nitrosourea, *N*-[*N'*-chloro-2-ethyl-N'-nitrosocarbamoyl]-*S*-methyl cysteamine sulfoxide (Perrimustine), is water soluble and has a high alkylating activity, similar to that of the widely used nitrosoureas BCNU and CCNU, and a low carbamoylating activity. Preclinical studies with a broad spectrum of murine tumors indicate that this new compound may be clinically useful. The maximally efficient dose range (MEDR) in L1210 bearing mice was 45 mg/m^2 (subcurative dose) to 67 mg/m^2 (subtoxic dose). The present phase I trial used an intrapatient escalation schedule, so that each patient entering the study received a potentially active dose. The first dose injected was 1:100 of the MEDR suboptimal dose to check for anaphylactic sensitivity. Patients were then given increasing doses at increasing time intervals until toxicity was observed. The highest dose was given on day 150–230. The main toxic effect was myelosuppression [five out of the 24 patients evaluated: one grade 4 thrombocytopenia, two grade 3 thrombocytopenia; anemia and leucopenia were milder (grade 1 to 2 on OMS scale)]. Of the 19 patients evaluated for clinical response, one showed response after the 45 mg/m^2 dose (disappearance of the cerebral metastasis with persistence of hepatic localizations in a patient with melanoma) and the disease was stabilized in two cases (a pleural mesothelioma and a renal carcinoma with lung metastases) after 26 and 37 weeks, with total cumulative doses per m^2 of 232 and 196 mg, respectively.

Key words: Cysteamine (2-chloroethyl) nitrosourea, intrapatient escalation scheme, Perrimustine, phase I.

Introduction

Nitrosourea compounds constitute an important family of antitumor drugs, the antineoplastic activity of which has been demonstrated for broad spectrum of experimental tumors as well as clinically in man.[1–5] However, despite international efforts and systematic programs[6–9] aimed at developing new derivatives with a better therapeutic index, relatively few agents are used in current clinical practice.

Two main problems limit their large scale clinical use: the possibility that nitrosoureas induce malignancies in man and, their most serious side effect, a dose-limiting myelosuppression.

Imbach *et al.*[10] synthesized a new 2-chloroethyl nitrosourea (CNCC) a mixture of cysteamine isomers based on rational structure–activity relationship studies. The activity of CNCC was demonstrated on experiments in a wide range of hematological malignancies and solid tumors.[11] Data on its *in vivo* metabolism in rats[6,12–14] led to the separation and synthesis of two metabolites *N'*-2(chloroethyl)-*N*-2 (methlysulfinyl) ethyl-*N'*-nitrosourea ($CMSOEN_2$ or Perrimustine) and *N'* - 2(chloroethyl) - *N* - 2 - (methylsulfonyl)ethyl-*N'*-nitrosourea ($CMSOE_2N_2$),[15,16] which both had experimental activity higher than the parent compound. Very promising results were obtained in mice bearing Lewis lung carcinoma, L1210 leukemia, L40 AKR leukemia, LCG C57 B16 lymphoma, B16 melanoma, colon 26 carcinoma and glioma 26.[17]

The present phase I clinical trial was conducted to identify the nature and the intensity of toxicity of Perrimustine administered in an intrapatient escalation schedule, in order to determine the optimal dose for phase II studies.

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Patients and methods

Twenty-five patients entered the study between June 1985 and October 1987. They all presented with histologically documented advanced malignancies. No restriction was made on the histological type of the tumors, which had all failed to respond to conventional therapy (Table 1).

Patients had a minimum life expectancy of 6 weeks and a performance status equal to or higher than 50% on the Karnofsky scale. None had been given therapy (chemo- or radiotherapy) for at least 4 weeks, and all had normal liver and renal function and almost all acceptable hematological parameters (leukocytes $\geq 4000/mm^3$, neutrophil count $>2000/mm^3$, hemoglobin ≥ 10 g% and platelet count $\geq 100\,000/mm^3$). The exceptions were three patients who had lower hematological values: one patient had a hemoglobin level of 9.8% and two patients had leukocyte counts below $4000/mm^3$, but both had a neutrophil count above $2000/mm^3$. The neutrophil count was therefore used as a guideline for hematological evaluation of these two patients rather than the total white blood cell (WBC) count. The patients were aware of the investigational nature of this study and of the possibility of secondary effects; informed consent was obtained from each of them.

Table 1. Patient characteristics

Number of patients entered	25
Number of patients evaluated	24
Sex (M/F)	15/10
Age range (years)	16–77
Tumor type	
melanoma	6
head and neck	4
breast cancer	1
lung cancer	2
corticosurrenaloma	1
colo-rectal	6
renal carcinoma	1
glioblastoma	1
unknown primary	1
mesothelioma	1
squamous cell epithelioma	1
Prior therapy	
chemotherapy	11
chemo- and radiotherapy	11
chemotherapy and other therapy	3
Prior nitrosoureas	5

Protocol

Perrimustine was prepared by Madelmont.[15,16] As suggested by the pharmacokinetic data obtained in mice and monkeys, the drug was dissolved in 125 ml of 5% glucose and delivered via a short 10–15 min perfusion.

The maximally efficient dose range (MEDR) was calculated from preclinical data in L1210 bearing mice.[12,17] The three doses of the MEDR reflected the suboptimal (45 mg/m^2), optimal (56 mg/m^2) and subtoxic (67 mg/m^2) doses. Acute animal toxicology results may be extrapolated to man as long as the protocols used are similar and dosages are expressed in the same units.[18–20]

Our original intrapatient escalation scheme[21,22] was adopted, as this scheme gives every patient entering the study a chance to receive a potentially active dose. All patients were first given 1:100 the MEDR suboptimal dose in order to check for any anaphylactic sensitivity. The interval between successive administrations was short up to 45 mg/m^2, after which it was 4–6 weeks in patients with no complications. This interval was prolonged in patients showing toxic effects until they had recovered.

The first intrapatient escalation scheme included 10 doses given over a period of 230 days. The number of doses was reduced to seven half way through the study since the toxicity was very mild and this phase lasted 150 days (Table 2).

Results

Of the 25 patients entering in the study, 24 were evaluated for toxicity and 19 were evaluated for clinical response. Only one patient received injections 8 and 9.

Non-hematological toxicity (Table 3)

Non-hematological toxicity was very mild. One patient with advanced carcinoma of the colon with lung, liver and peritoneal metastases complained of abdominal pain. The pain generally began 8–10 days after each administration, lasted 2–3 days, and required analgesic therapy. The relationship of the pain to the toxic effect of the drug may be questioned, because of the advanced stage of the disease.

Nausea and vomiting were frequent but always tolerable (grade 1). They lasted a few hours after

Table 2. Dose escalation

	First scheme			Second scheme		
Day	interval (days)	dose (mg/m^2)	TCD (mg/m^2)	interval (days)	dose (mg/m^2)	TCD (mg/m^2)
1		0.45	0.45		0.45	0.45
2	1	4.50	4.95	1	4.50	4.95
7	5	9	13.95	5	22.50	27.40
35	28	15	28.95	28	37.50	64.90
63	28	22.50	51.40	28	45	109.90
90	28	30	81.40			
105				42	56	165.90
118	28	37.5	118.90			
146	28	45	163.90	42	67	232.90
188	42	56	219.90			
230	42	67	286.90			

Table 3. Non-hematological toxicity

Injected dose (mg/m^2)	No. of patients	No. of patients with toxicity	Type of toxicity
22.5	25	0	—
22.5	17	1	abdominal pain grade 1
30	5	1	nausea and vomiting grade 1
37.5	10	2	nausea and vomiting grade 1
		1	creatinin grade 1
45	16	2	nausea and vomiting grade 1
		1	alopecia grade 1
56	8	2	nausea and vomiting grade 1
67	4	0	—

drug administration and were manageable with standard antiemetic regimens. Alopecia (grade 1) on the WHO scale occurred in one patient with melanoma after the 45 mg/m^2 injection; there was transient elevation of creatinin (grade 1) in another patient after the 37.5 mg/m^2 dose.

Hematological toxicity (Table 4)

As for most of the nitrosourea derivatives known to date, the main toxic effect in this study was myelosuppression. Hematological toxic effects were graded using the WHO criteria. Five patients

Table 4. Hematological toxicity

Dose level (mg/m^2)	No. of patients	No. of patients with toxicity	Type of toxicity
22.5	25	0	
22.5	17	1	thrombopenia grade 1
30	5	1	thrombopenia grade 1
37.5	10	1	neutropenia grade 1
45	16	2	neutropenia grade 2 thrombopenia grade 4
56	8	2	neutropenia grade 1 thrombopenia grade 1
67	4	3	anemia grade 2 neutropenia grade 1 thrombopenia grade 3

Table 5. Characteristics of patients with hematological toxicity

Age/sex	Diagnosis	Prior therapy	Dose level (mg/m^2)	TCM (mg/m^2)	Toxicity	Clinical response
36/M	colon	5FU-ADM-I-OHP-MTC	22.5	50	thrombopenia grade 1	
			30	80	thrombopenia grade 1	
			45	125	thrombopenia grade 1	
58/M	mesothelioma	VDS-ADM-5FU-CPM	37.5	64	neutropenia grade 1	
		VCR-VP16-CDDP	37.5	101.5	neutropenia grade 2	stabilization
			45	146.5	neutropenia grade 1	
			56	202.5	neutropenia grade 1	
36/M	melanoma	DTIC-I-OHP-AZIMEXON	56	127	thrombopenia grade 3	
44/M	colon	5FU-FOL	56	184	anemia grade 1	
			67	251	anemia grade 2	
43/M	melanoma	DTIC-CCNU-BCNU-ADM	56	220	thrombopenia grade 2	dissociated response
		VCR-I-OHP	67	287	thrombopenia grade 3	

developed bone marrow toxicity of varying types and intensities (Table 5). Anemia was observed in one patient. It was first evaluated as grade 1 at 3 weeks after the 56 mg/m^2 dose [total cumulative dose (TCD): 184 mg/m^2] and had normalized 3 weeks later just prior to giving the patient the next dose (67 mg/m^2 level with a TCD of 251 mg/m^2). Grade 1 anemia reappeared earlier (day 14) after drug administration, with intensification and nadir value (grade 3) on day 31. Treatment was discontinued after a total of seven doses because of disease progression.

One of the two patients who entered the study with a low WBC count but normal neutrophil count developed neutropenia after the 37.5 mg/m^2 dose, which continued through the 56 mg/m^2 dose. Grade 2 neutropenia appeared after four doses, grade 1 only after the fifth, sixth and seventh doses, while the disease was stabilized (pulmonary X-rays and tomodensitometry).

Three of the 24 patients evaluated presented grade 1 to 4 thrombopenia. This was the most troublesome and dose-related toxic effect encountered in this study.

Patient no. 1 (adenocarcinoma of the sigmoid with liver and peritoneal metastases) entered the study with the lowest performance status. He developed grade 1 thrombopenia on the 12th day after the fifth dose (22.5 mg/m^2 dose, first scheme) and 1 week after the sixth dose (37 mg/m^2), which normalized 2 weeks later. The next dose (45 mg/m^2) was followed by grade 4 thrombopenia. Treatment was discontinued. The hematological toxicity might have been due to the poor performance status of the patient.

Patient no. 3 [melanoma of the trunk (Clark III) diagnosed 5 years ago] entered the study with metastases in the abdominal wall and enormous inguinal adenopathies. He received a total of five courses; the highest dose was 56 mg/m^2. Grade 3 thrombopenia appeared 5 weeks after the 56 mg/m^2 dose. Treatment was discontinued as the disease progressed rapidly.

Patient no. 5 (melanoma of the trunk diagnosed 9 years ago) entered the study with a good performance status, in spite of a very advanced disease, with liver (post-resection of the right lobe) and brain metastasis. He was given nine doses including the highest dose (67 mg/m^2) for a TCD of 285 mg/m^2 over a period of 29 weeks. The doses were well tolerated up to 45 mg/m^2, when he presented mild hair loss. Grade 1 thrombopenia appeared 35 days after the 56 mg/m^2 dose (day 190) with normalization of the platelet count 1 week later. The patient was then given the next dose (67 mg/m^2). Grade 3 thrombopenia occurred 27 days later. This patient's blood 5′-cysteil DOPA level dropped to zero and the cerebral metastasis disappeared; however, the hepatic metastases continued to progress. This might be considered as a dissociated response to the treatment.

Clinical response

Of the 24 patients evaluated for toxicity in this phase I study, 19 were also evaluable for response, with objective response in three patients.

Two patients, a mesothelioma of the pleural cavity (Figure 1) and a renal carinoma with lung

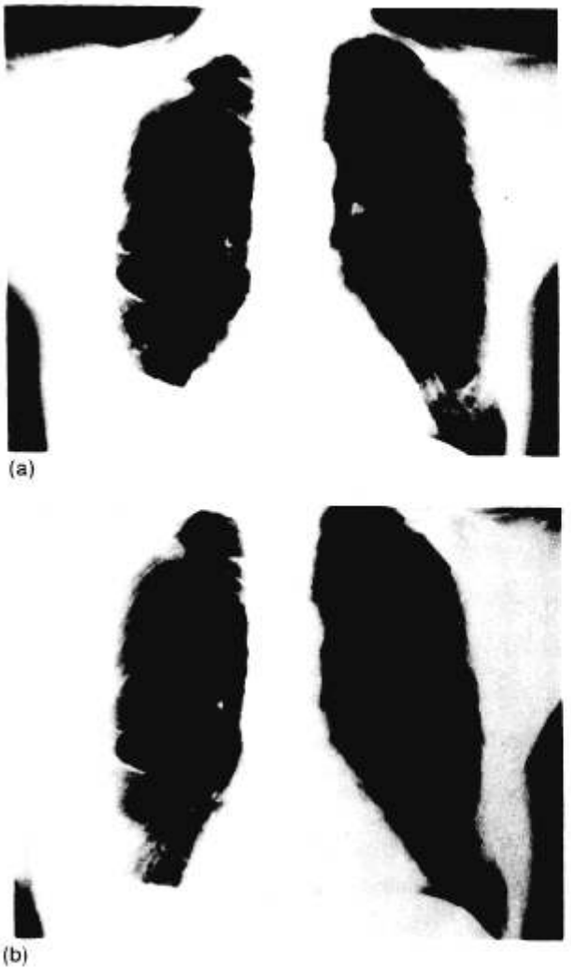

Figure 1. Patient M.A. (aged 58 years): mesothelioma. (a) Before treatment [30 April 1986]. (b) After 4 courses, TCD: 116 mg/m^2 [3 July 1986].

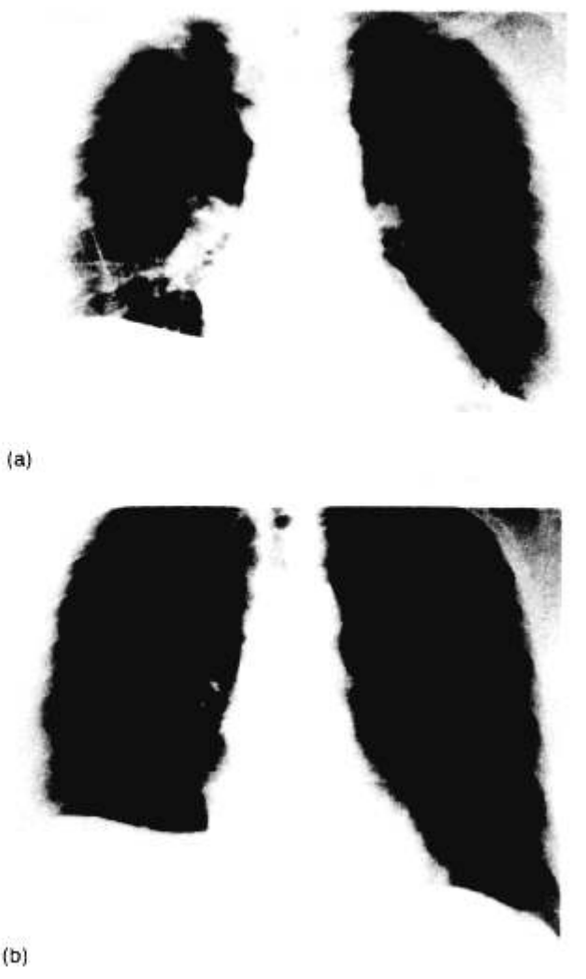

Figure 2. Patient L.G.M. (aged 46 years): renal ADC with pulmonary metastasis. (a) Before treatment [9 September 1986]. (b) After 7 courses, TCD: 232 mg/m^2 [1 April 1987].

metastasis (Figure 2) presented a stabilization of the disease, observed for 37 and 26 weeks with a TCD of 196 and 232 mg/m^2, respectively, as judged by clinical evaluation, chest films and tomographies. The renal carcinoma patient showed no toxic effects.

A dissociated response was seen in the third patient with the disappearance of cerebral metastasis but persistence of hepatic metastases.

Discussion

The present work addresses two questions: the toxicity of a new nitrosourea and the use of an 'intrapatient escalation scheme'.

The intrapatient escalation scheme is justified by the fact that the lowest doses given the first groups of patients in conventional trials in order to follow the development of toxicity seldom have any oncostatic activity. This results in the inefficient management of the patients available for study, as no useful information is obtained from these patients, and, most importantly, these same patients have no chance of benefiting from the drug under trial.

The possible cumulative toxicity was minimized by leaving a reasonable interval between injections. Under those conditions, i.e. after repeated injections, a lack of toxic response or a mild response is additional evidence of the low toxicity of the drug.

The subcurative dose in mice was defined prior

to administration to patients. The patients were then given 1:100 of that dose to check for anaphylactic sensitivity. This was followed by 1:10 of the mouse subcurative dose.

The subsequent doses were obtained by multiplying the preceeding values to produce Fibonacci series, the biological significance of which is suggested by the observation that on the stem of plants, insertion of the leaves diverges and this divergence has a constant value for a given species. The Fibonacci series describes the most frequent type of phyllotaxic organization.[23,24]

Although the patients in this phase I trial were a heterogeneous group in terms of tumor type and/or host factors, and prior therapy may well have modified the response of the patients, the limiting side effect was generally hematological toxicity, as observed in other clinical trials with nitrosourea analogs.

No cumulative effects were observed since the intrapatient escalation scheme used in this study showed no toxicity greater than that found in other studies on nitrosourea analogs which followed the classical Fibonacci scheme.[2,6,8,24,25]

Of the patients taking part in the study, 14 received the therapeutic dose. This number of patients would not have been so treated using the classical Ficonacci scheme with the same total number of patients. Since only two of these 14 patients showed any hematological toxicity, the optimal dose of the MEDR of this study may be considered safe and may be recommended as a starting dose for phase II trial.

Three objective clinical responses were obtained (one dissociated response and two stabilizations). Better clinical results might be expected with more carefully selected patients, who could perhaps be given higher doses, followed by autologous bone marrow rescue.[26]

Acknowledgments

We thank Dr S Orbach-Arbouys for constructive criticism and Mrs Marie-Jo Ferreira for secretarial assistance.

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(Received 11 February 1992; accepted 10 March 1992)