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Corynebacterium parvum Toxicity in Patients with Limited and Advanced Malignancy*

YASHAR HIRSHAUT,†‡ CARL M. PINSKY,† HARRY J. WANEBO§ and DAVID W. BRAUN, Jr.||

†*Clinical Immunology Service, Department of Medicine, Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY* 10021, *U.S.A.*, §*Department of Surgery, University of Virginia School of Medicine, Charlottesville, VA, U.S.A. and* ||*Biostatistics Laboratory, Memorial Sloan-Kettering Cancer Center, New York, NY* 10021, *U.S.A.*

Abstract—*The toxicity of intravenously administered* Corynebacterium parvum *was observed in* 14 *patients with stage II melanoma and in* 14 *patients with advanced ovarian carcinoma. Those with melanoma were rendered disease-free by surgery prior to treatment. The ovarian cancer patients had failed chemotherapy with alkylating agents and were receiving* C. parvum *prior to chemotherapy as part of an immunochemotherapy trial. Both clinical and laboratory parameters were observed. The mean daily* C. parvum *dose for melanoma patients was* 2.03 mg/m^2 *and for ovarian carcinoma patients* 2.02 mg/m^2. *The most important clinical toxic effects noted were fever, chills, blood pressure changes, headache, nausea, vomiting and diaphoresis. Laboratory toxicity was mild, with small decreases in hemoglobin levels, white blood cell counts and uric acid and albumin concentrations occurring in some patients. Serum bilirubin and SGOT levels tended to rise. In addition to determining the frequency of clinical toxic effects by treatment course, consideration was also given to frequency per treatment day, correlation of the occurrence of different toxicities in the same patient, time of onset of each toxicity and, for vital signs, to intensity of change and duration. In this analysis no major differences in toxicity were observed when* C. parvum *was given to the two patient groups.*

INTRODUCTION

ALTHOUGH efforts to develop effective immunotherapy for human cancer during the last decade have given generally disappointing results, the large numbers of therapeutic trials undertaken during this time have provided considerable new information about the biological effects of immune response modifiers in man. Some of these effects, such as fever and alterations in blood pressure, are common to many of the agents in this pharmaceutical category. Fever, for instance, has been found to follow treatment with bacterial products, interferon inducers and interferon preparations themselves. It may be that these common events reflect the need for modulators of immunity to follow a final common pathway. Of the putative immunopotentiators most thoroughly studied during the last 10 yr, *Corynebacterium parvum* is one of those which most consistently has shown immunoadjuvant and antitumor effects in experimental animal systems [1–9]. In man, Hilal *et al.* [10] have found that *C. parvum* is also capable of effecting immune function in a predictable manner. Unfortunately, from a clinical standpoint this agent has been less than satisfactory, although there have been occasional favorable reports [6, 11, 12] about its therapeutic efficacy against some forms of human cancer, particularly when used to augment concurrent chemotherapy. We have studied the toxicity of this drug in detail, and as a prototype of biological immune response modifiers, the data obtained continues to be timely for those designing future trials of agents intended to exert their antitumor effects indirectly through modifying the biological responses of the host.

This paper represents an analysis of a portion of the available data base regarding the toxicity of *C. parvum*. It deals specifically with the relative frequency and intensity of toxic manifestations noted in patients with limited and extensive

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‡To whom requests for reprints should be addressed.

malignant disease. One study group consists of patients with recently resected, stage II melanoma [10] who are apparently free of disease. The other group consists of women with extensive recurrent, unresectable carcinoma of the ovaries [2].

MATERIALS AND METHODS

Patients

All patients received *C. parvum* while inpatients at Memorial Hospital for Cancer and Allied Diseases, New York. The *C. parvum* was supplied as a formalin-killed preparation by the Burroughs Wellcome Co. through the courtesy of Dr J. K. Whisnant. The patients were entered in one of two study protocols, as described below. Patients with malignant melanoma had complete resection of primary tumor and regional lymph node metastases and were disease-free when started on treatment. Those with ovarian carcinoma had stage III or IV disease which had failed therapy with alkylating agents and/or radiation therapy. Only patients with measurable disease were entered into the trial.

Study protocols

Patients with ovarian carcinoma were entered in a randomized study to compare the efficacy of immunochemotherapy vs chemotherapy alone. Those selected to receive immunotherapy were first given *C. parvum* i.v. for 14 days, utilizing a slowly escalating dose scheme with a minimum dose of 1 mg and a maximum dose of 20 mg administered daily. All patients then received a combination of adriamycin, cyclophosphamide and 5-fluorouracil [7]. Data on the clinical toxicities associated with *C. parvum* were collected in a group of 14 patients. Because these patients had advanced disease it was decided to compare the toxicities observed to those experienced by a healthier population.

The melanoma study [10] was intended to determine the efficacy of *C. parvum* in preventing recurrence of disease among patients with regional metastases (stage 11) whose disease had been completely resected by surgery. Treatment began 10 days–2 months after surgery. *Corynebacterium parvum* was administered i.v. at a dose of 4 mg daily for 5 days followed by the same dose given.s.c. weekly for 1 yr, every 2 weeks for the second year and every 4 weeks for a third year. Doses were reduced when excessive fever, chills, malaise or severe local cutaneous reactions were encountered. Fourteen of 60 melanoma patients treated were selected at random to provide the desired comparison group. Clinical toxicity data similar to that collected for the ovarian group were extracted from the records of the melanoma patients. Not surprisingly, fewer data were available retrospectively than had been collected prospectively in the ovarian group. Nevertheless, statistical comparisons could be made.

Patient observation

Immediately prior to treatment and for approximately 6 hr after each dose of intravenous *C. parvum* patient were attended by a study nurse, who elicited subjective complaints from the patient and measured vital signs at minimum intervals of 30 min until stable. Once stable, measurements were taken hourly. Following these 6 hr of close observation the regular nursing staff continued to measure vital signs every 2 hr, for a total study period of 24 hr. Laboratory measurements of toxicity included blood counts, biochemical screening profiles, 5′ nucleotidase and urinalysis. For those in the melanoma study such laboratory tests were performed before the first dose of *C. parvum* and then on days 2, 4–5 and 14. The same tests were performed for individuals with ovarian carcinoma pretreatment and on days, 3, 5, 7, 10, 12, 15 and 28.

Statistical methods

The frequency of clinical toxic effects of *C. parvum* were calculated on both a per patient and a per day of treatment basis. This provides a measure of how many patients experienced a particular toxic effect and how often during the course of therapy the effect was seen. The time of onset of toxic effects was also studied. For this analysis only days on which the effect was observed are included. In addition to calculating mean time of onset, the 75th percentile is also reported. This value is important because the range of times varied considerably; the 75th percentile provides a good measure of the time interval during which a patient is likely to experience a particular toxic effect, if the patient will experience it at all. All possible 2×2 tables formed by comparing the presence or absence of any pair of clinical toxic effects were evaluated for statistically significant correlations. Because of the great number of significance tests performed, the nominal significance levels are difficult to interpret, but they serve as a useful guide to the possible importance of the reported 'significant' pairs of clinical toxic effects.

Vital signs were recorded frequently during the course of therapy. No patterns were observed with respect to dose level and no clear differences were seen among the patients. Therefore the data were collapsed across treatment days and patients. Mean values and 95% confidence intervals were calculated for each hourly interval following the start of the infusion (if only one measurement was

made in a time period, a confidence interval cannot be calculated).

Finally, important changes in laboratory values were sought by establishing baseline values for each patient using data collected prior to the course of therapy. Subsequent changes in the levels of these values (laboratory toxicities) were evaluated by comparison to baseline values using the paired *t* test. As before, the great number of significance tests performed makes the nominal significance levels difficult to interpret. Nonetheless, these significance levels are useful for evaluating the magnitude of average changes from baseline in the light of the variability across patients.

RESULTS

There were 14 patients in each group (Table 1). The mean age of the melanoma patients was 44 (21–59) and that of patients with carcinoma of the ovary was 50 (29–63). In the melanoma group there were 12 male and 2 female patients.

Daily doses of *C. parvum* administered to patients in both groups were similar. As shown in Table 2, the mean daily dose was 2.03 mg/m^2 for those with melanoma and 2.02 mg/m^2 for women with carcinoma of the ovary. The mean maximum doses per m^2 were also similar, being 2.15 mg/m^2 for melanoma and 3.70 mg/m^2 for carcinoma of the ovary. As anticipated from the protocols, however, the dose range was greater for the ovarian carcinoma group, as was the total dose received. The total *C. parvum* dose for melanoma patients was 8.84 mg/m^2 (2.00–11.68) and for ovarian carcinoma patients 26.12 mg/m^2 (9.29–121.93).

The 13 most common clinical toxic effects of *C. parvum* are presented in Table 3. This table summarizes all observations made for each patient while they participated in their respective studies. Nearly all patients experienced chills, usually shaking chills. Also frequent were headache, nausea, vomiting and diaphoresis. Overall, the incidence of clinical toxicity was higher in the ovarian carcinoma group. These patients received 14 days of treatment vs 5 days for those with melanoma.

The frequency of toxic effects in relation to treatment days is shown in Table 4. The incidence of most toxicities is similar in both groups. Patients with resected melanoma were less likely

Table 1. Study population

	Ovarian carcinoma	Melanoma
Age		
Mean	50	44
Range	29–63	21–59
Sex		
Male	0	21
Female	14	2
Total patients entered	14	14

Table 3. Clinical toxicity of C. parvum *infusions*

Toxicity	Ovarian carcinoma *	%	Melanoma *	%
Chills	14/14	100	10/13	77
Shaking chills	11/14	79	12/13	92
Nausea	11/14	79	2/13	15
Headache	10/14	71	7/13	54
Malaise	9/14	64	1/13	5
Diaphoresis	8/14	57	9/13	69
Pain	8/14	57	7/13	54
Emesis	5/14	36	6/13	46
Cyanosis	4/14	29	8/13	62
Facial pallor	4/14	29	1/13	5
Generalized aches	4/14	29	2/13	15
Dyspnea	3/14	21	0/13	0
Color flushed	3/14	21	1/13	5

* = $\frac{\text{No. affected}}{\text{No. treated}}$.

Table 2. Doses administered

	Ovarian carcinoma	Melanoma
Patients treated	14	14
Average number of doses	13 (4, 14)*	4 (1, 5)
Average total dose (mg)	56 (8, 177)	16 (4, 20)
Average total dose (mg/kg)	1.015 (0.23, 4)	0.23 (0.05, 0.33)
Average total dose (mg/m^2)	26.12 (9.29, 121.93)	8.84 (2, 11.68)
Average daily dose (mg)	4.20 (1.14, 12.64)	3.8 (2.8, 4)
Average daily dose (mg/kg)	0.096 (0.02, 0.29)	0.05 (0.03, 0.07)
Average daily dose (mg/m^2)	2.02 (0.66, 8.71)	2.03 (1.34, 2.34)
Average maximum dose (mg)	8 (3, 25)	4 (4, 4)
Average maximum dose (mg/kg)	1.10 (0.04–11.50)	0.60 (0.05, 0.07)
Average maximum dose (mg/m^2)	3.70 (1.74–17.22)	2.15 (1.92, 2.36)

*(,) = range.

Table 4. Frequency of toxic effects of C. parvum *infusions in relation to total treatments*

Toxicity	Ovarian carcinoma: No. of occurrences		Melanoma: No. of occurrences	
	Total treatments	%	Total treatments	%
Chills	88/175	50.3	21/59	35.6
Shaking chills	67/175	38.3	37/59	62.7
Nausea	23/175	13.1	2/59	3.4
Headache	35/175	20.0	18/59	30.5
Malaise	25/175	14.3	1/59	1.7
Diaphoresis	18/175	10.3	13/59	22.0
Pain	28/175	16.0	14/59	23.7
Emesis	24/175	13.7	9/59	15.3
Cyanosis	6/175	3.4	17/59	28.8
Facial pallor	4/175	2.3	1/59	1.7
Generalized aches	6/175	3.4	2/59	3.4
Dyspnea	5/175	2.9	0/59	0.0
Color flushed	5/175	2.9	1/59	1.7

to complain of malaise and somewhat more likely to experience cyanosis.

To understand more about the pathophysiology of *C. parvum* toxicity the mean time of onset of each toxicity was calculated. Since the range of this measurement varied considerably for some of the toxic effects, the time when 75% or more of treated individuals had experienced a given toxicity is also presented in Table 5. The wide range in times of onset is indicated by the standard error of measurements given in Table 1 and is further illustrated in Figs 1 and 2. The time of onset of shaking chills ranges from 1 to 4½ hr, or a span of 3½ hr (Fig. 1), while the time of onset of headaches ranges from 1½ to 10½ hr after treatment: a time span of 9 hr (Fig. 2). More than 55% of shaking chills begin during the second hour after treatment. In contrast, the number of patients developing headache in any 1-hr period was under 15%.

When the time of onset of toxicities is considered according to mean time of onset there appear to be four sequential sets of toxic

Table 5. Time of onset of clinical effects following C. parvum *infusions for ovarian carcinoma and melanoma*

Toxicity	Affects ≥75% of patients (hr)	Time of onset		
		Mean	S.E.	*n**
Chills	2.58	2.19	0.117	109
Shaking chills	2.28	2.28	0.08	104
Nausea	5.00	4.34	0.49	25
Headache	6.07	4.35	0.33	53
Malaise	5.50	4.38	0.48	26
Diaphoresis	7.33	6.27	0.51	31
Pain	3.50	3.20	0.34	42
Emesis	3.38	3.05	0.35	33
Cyanosis	3.17	2.07	0.20	23
Facial pallor	5.23	5.35	1.99	5
Generalized aches	5.15	4.18	0.43	8
Dyspnea	3.07	2.30	0.60	5
Color flushed	6.00	6.28	0.82	6

*n = No. of observations.

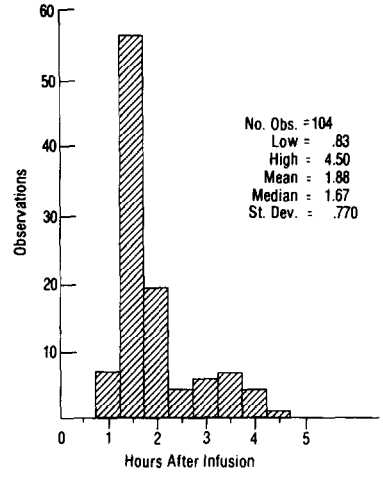

Fig. 1. Time of onset of shaking chills.

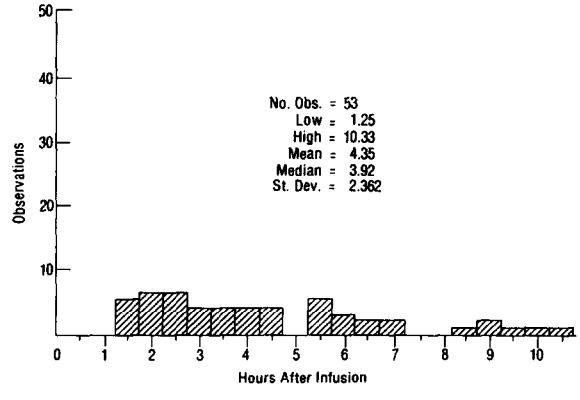

Fig. 2. Time of onset of headache.

manifestations. After a mean of 2 hr patients are noted to develop cyanotic sking changes, which are soon followed by chills or shaking chills accompanied by dyspnea, emesis and pain. These complaints last for 30 min–1 hr and then the patients begin to notice diffuse aching, nausea, headache and a sense of malaise. As these symptoms in turn subside the patients become pale and diaphoretic and finally begin to flush.

Alternatively, if the sequence of onset of symptoms is considered according to the time when 75% or more of the patients develop toxicity only two distinct phases of toxic changes can be discerned. The earliest toxic sign is chills. Shaking chills, when they occurred, occurred in more than 75% of the patients by 2½ hr and a generalized sense of chilliness by 3 hr. Chills are associated with dyspnea, cyanosis, emesis and complaints of diffuse muscle ache. By 4 hr this phase is completed. One hour later the second phase of toxicity begins. The patients experience a 2-hr period of nausea, aches, pallor, malaise, flushing, headache and the development of diaphoresis.

Statistically significant correlations of clinical toxic manifestations are listed in Tables 6 and 7. Some of the correlations appear obvious, others might not be anticipated on the basis of the time of onset sequence. For instance, the strong correlation of shaking chills with cyanosis can be explained as due to the vasoconstrictive effects associated with chilling. On the other hand, while there is an association between shaking chills and diaphoresis, these occur about 5 hr apart. Nausea and emesis are, of course, closely associated. However, emesis occurs before nausea, so the two may be generated independently.

Table 6. Significant correlations of toxic clinical manifestations

Toxicity A	with Toxicity B	*P*
	Ovarian carcinoma	
Shaking chills	chills	<0.0001
Shaking chills	emesis	0.05
Shaking chills	pain	0.014
Nausea	emesis	<0.0001
Emesis	pain	0.005
Generalized aches	malaise	0.05
Malaise	color flushed	0.02
	Melanoma	
Shaking chills	chills	<0.0001
Shaking chills	headache	0.014
Shaking chills	diaphoresis	0.005
Shaking chills	cyanosis	0.02
Chills	diaphoresis	0.04
Chills	cyanosis	0.03
Headache	emesis	0.03
Diaphoresis	pain	0.01

Additional insight into the biologic effects of *C. parvum* treatment comes from consideration of vital sign changes. The ranges of these changes in relation to temperature, blood pressure and pulse are shown in Table 8. Peak temperatures observed after *C. parvum* infusion ranged from 38.5 to 40.7°C in patients with ovarian cancer and from 38.3 to 41°C in those with melanoma. The mean peak systolic pressures tended to be higher for those with melanoma: 254 vs 190 mm Hg. Similarly, peak diastolic pressures were higher in the melanoma group: 160 vs 120 mm Hg. In contrast, peak pulse rates were highest in patients with carcinoma of the ovary: 176 vs 152. Figure 3 compares the mean temperatures of treated patients in each group by hourly intervals following infusion. The data points are means of temperatures recorded for all patients over all dosages. Peak temperatures are almost identical in both study groups and are achieved in each instance after 5 hr. They then fall to normal by 15 hr. Changes in blood pressure following treatment are shown for ovarian carcinoma in Fig. 4 and for melanoma in Fig. 5. Peak blood pressures occur considerably earlier than peak temperatures. Systolic and diastolic pressures in both those with ovarian carcinoma and melanoma peak at 2 hr. The mean systolic pressure is higher for those with melanoma than ovarian carcinoma: 144 vs 123. Blood pressures return to normal values within 4–5 hr.

Pulse rate changes in *C. parvum* infusion are illustrated in Fig. 6. Peak pulse rate for those with ovarian cancer occurred at 5 hr and for those with melanoma at 4 hr. Pulse rates fell more rapidly for those with ovarian cancer and returned to normal by 12 hr. For melanoma patients baseline values were not reached until about 14 hr.

The laboratory toxicity of intravenous *C. parvum* as observed in this analysis was relatively mild. In ovarian cancer patients the only significant change from baseline was a fall in

Table 7. Significant correlations of toxic clinical manifestations in ovarian carcinoma and melanoma

Toxicity A	Toxicity B	*P*
Shaking chills	emesis	0.01
Shaking chills	diaphoresis	0.0002
Shaking chills	pain	0.007
Shaking chills	generalized aches	0.03
Shaking chills	cyanosis	<0.0001
Chills	diaphoresis	0.02
Chills	cyanosis	0.006
Headache	pain	0.04
Headache	cyanosis	0.02
Nausea	emesis	<0.0001
Emesis	pain	0.006
Diaphoresis	cyanosis	0.004

Table 8. Range of changes observed in vital signs

Patient	Temperature Low	Temperature High	Blood pressure Systolic Low	Systolic High	Diastolic Low	Diastolic High	Pulse Low	Pulse High
	35.7	40.7	70	150	48	100	70	148
	35.1	37.7	84	140	40	100	76	160
	34.9	39.9	90	190	56	120	68	128
	36.2	40.0	86	130	48	90	76	136
	36.1	40.3	70	148	10	90	64	132
	35.8	40.2	80	132	50	90	80	122
Ovarian	36.7	40.7	104	184	60	110	80	132
carcinoma	36.5	38.5	80	170	60	120	88	148
	36.5	38.8	100	180	60	106	100	176
	35.4	39.1	90	172	60	110	70	120
	35.4	39.2	94	148	50	90	72	136
	35.0	40.5	80	150	50	100	80	172
	36.4	40.7	80	138	50	80	80	140
	36.0	40.2	86	170	30	100	72	140
Overall	34.9	40.7	70	190	10	120	64	176
	36.2	39.3	100	150	70	98	76	104
	36.5	40.5	82	124	50	80	84	146
	37.0	40.6	102	164	54	90	80	140
	36.8	39.5	110	140	64	90	64	112
	37.1	40.0	128	170	60	110	80	112
	36.4	40.5	120	220	80	110	72	120
Melanoma	37.2	40.0	100	150	50	90	72	112
	36.2	40.7	100	164	40	110	80	128
	36.2	40.5	90	156	40	96	72	120
	36.0	39.9	74	170	30	100	72	144
	36.5	40.3	89	170	50	90	78	152
	36.0	40.0	100	254	60	128	80	152
	36.1	39.5	90	148	60	90	68	116
	35.4	41.0	100	250	50	160	60	132
Overall	35.4	41.0	74	254	30	160	60	152

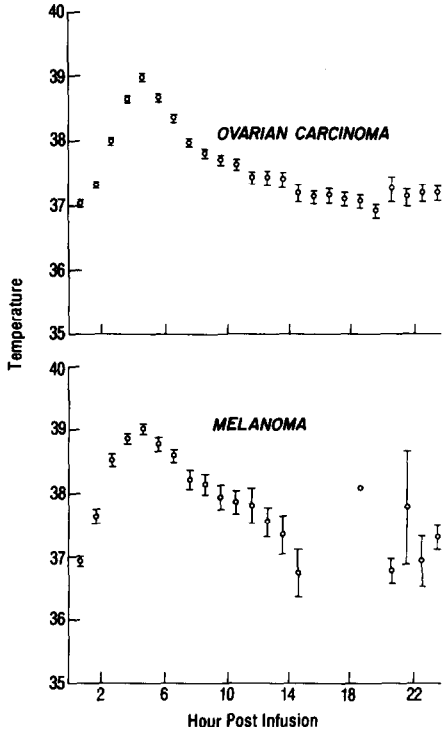

Fig. 3. Temperature response to C. parvum *infusion.*

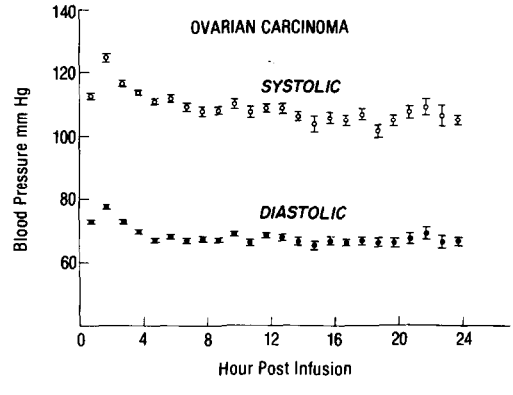

Fig. 4. Blood pressure response to C. parvum *infusion in ovarian carcinoma.*

platelet counts ($P<0.01$, paired t test) noted by 4–7 days and a decrease in hemaglobin observed between 15 and 23 days ($P<0.01$). Among those with resected melanoma significant ($P<0.05$) falls in total white blood cell counts, uric acid levels and total protein and albumin values were observed by 1–3 days, as were increase in bilirubin ($P<0.01$) and SGOT ($P<0.05$) levels. After 4 days significant decreases ($P<0.01$) were seen in

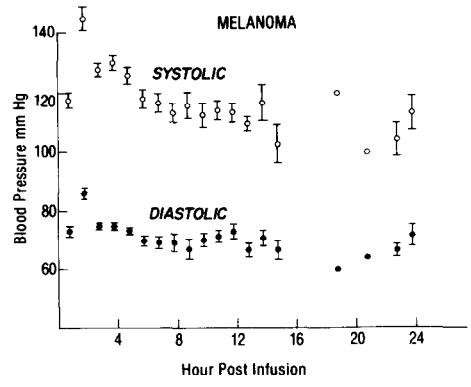

Fig. 5. Blood pressure response to C. parvum *infusion in melanoma.*

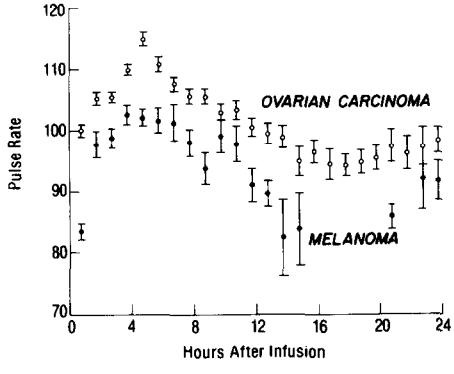

Fig. 6. Changes in pulse rate following C. parvum *infusion.*

hemaglobin levels and white blood cell and platelet counts, as well as in uric acid, total protein and albumin concentrations. Alkaline phosphatase and SGOT values rose further.

DISCUSSION

In preliminary reports [13, 14] we have previously summarized the clinical and laboratory toxicity of *C. parvum*. These observations were consistent with those reported by Wooodruff and Boak [15], who were the first to use this agent intravenously in the treatment of cancer. They have since been confirmed by many others [1, 5, 8, 16]. The more extensive evaluation in this paper confirms and extends previous observations, providing more quantitative information about frequency, timing and association of toxic signs and symptoms. Overall no major differences in toxicity were observed in the present analysis when *C. parvum* was given to patients with no evidence of residual cancer versus patients with extensive remaining disease. The differences that were noticed, e.g. greater malaise, nausea and higher pulse rates after *C. parvum* treatment of ovarian carcinoma patients, are all consistent with the more debilitated condition of those with ovarian carcinoma. The magnitude of the difference in toxicities found in those with limited vs extensive disease did not preclude the use of *C. parvum* in those with more serious illness. Indeed, by this time it is clear that while *C. parvum* does have significant side-effects these are relatively modest when compared to those of other anticancer drugs.

In our previous reports [13, 14] we proposed that most of the toxic changes observed clinically could be accounted for by a two-phase response to *C. parvum* administration. The first of these starts to occur 60–90 min after drug infusion with chills, associated muscular spasms and vasoconstriction. Increased muscular tonus and vasoconstriction would account for most of the symptoms and signs seen such as cyanosis, dyspnea, emesis and increases in blood pressure and, to a lesser extent, pulse rates. With the subsequent onset of fever and vasodilatation one observes headache, pallor and diaphoresis, leading to flushing, general achiness, malaise, nausea, mild decreases in blood pressure

Table 9. Laboratory toxicity in ovarian carcinoma

Test	Pre RX	Change from baseline Days 1–3	Days 4–7	Days 8–14	Days 15–23
LYMP	15.5 (4)	-5.30 (3)	-1.2 (4)	3.0 (3)	-12.00 (2)
HGB	11.1 (14)	-0.05 (13)	-0.68 (14)	-1.1 (13)	-2.10**(12)
WBC	5.2 (14)	-0.06 (13)	-0.78 (14)	-0.05 (13)	4.90 (11)
PLAT	252.0 (12)	-12.00 (11)	-88.00**(11)	-76.00**(11)	-62.00**(9)
BUN	11.5 (13)	0.50 (10)	0.60 (8)	0.00 (10)	2.50 (4)
URIC	4.2 (13)	-0.21 (9)	7.40 (8)	-0.17 (10)	-0.30 (4)
TPROT	6.3 (13)	0.01 (9)	6.90 (8)	-0.05 (10)	0.50 (4)
ALBU	3.6 (13)	0.11 (9)	-0.01 (8)	-0.23 (10)	-0.32 (5)
BILI	0.9 (13)	0.19 (9)	0.24 (8)	0.60 (10)	0.48 (4)
ALK	14.9 (13)	-1.70 (9)	-1.20 (8)	-2.50 (10)	1.74 (5)
SGOT	37.3 (13)	8.40 (9)	30.00 (8)	4.50 (10)	26.20 (4)
5'NT	8.5 (2)	-1.00 (2)		4.50 (2)	
NEUT	75.0 (4)	0.33 (3)	-5.00 (4)	-4.00 (3)	-7.7 (3)

* $P<0.05$.
** $P<0.01$.

Table 10. Laboratory toxicity in melanoma

Test	Mean Pre RX	Change from baseline Days 1–3	Days 4–7
HGB	13.36 (14)	0.51 (12)	-1.52**(11)
WBC	9.80 (6)	-2.80* (6)	-3.60* (5)
PLAT	343.00 (14)	-91.00 (11)	-119.00**(10)
BUN	11.40 (5)	-1.00 (3)	1.00 (2)
URIC	5.90 (13)	-1.30 (7)	-1.10**(6)
TPROT	7.30 (13)	-0.56* (7)	-0.88**(6)
ALBU	4.40 (13)	-0.40* (7)	-0.68**(6)
BILI	0.43 (13)	0.29**(9)	0.20 (7)
ALK	6.20 (13)	3.70 (9)	4.40* (8)
SGOT	29.00 (13)	49.00* (9)	87.00**(8)
5'NT	7.60 (7)	9.20 (4)	12.00 (2)

* = $P < 0.05$.
** = $P < 0.01$.

and further increases in pulse rate. The current analysis does not disagree with this overall picture but suggests that there is considerable variation between patients in their susceptibility to the toxic effects of *C. parvum* and their patterns of response.

Studies of the toxicity of any new antitumor agents generate a relatively large amount of data whose collection is time-consuming and whose comprehensive analysis is becoming increasingly difficult because of the many variables being measured simultaneously. Evaluating the toxicity of immunotherapeutic drugs may be even more difficult since some of the 'toxic' effects of these agents may reflect pharmacologic effects on the immune system which may be therapeutically desirable. The current analysis, which had the benefit of both the computer and biostatistician, breaks new ground by demonstrating the capacity of newer data processing systems to handle and analyze the relatively large quantity of data generated in phase I drug studies. Thus information is provided not only about the nature and overall frequency of each toxic symptom and sign but also about its likelihood to occur during a given treatment, its association with other toxic manifestations, time of onset, intensity and duration. Such information permits more accurate prediction of the toxicity to be expected in later clinical trials and also may shed some light on the physiologic changes which underlie the observed toxic effects of an agent.

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