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Corynebacterium parvum followed by Chemotherapy (Actinomycin D and DTIC) compared with Chemotherapy Alone for Metastatic Malignant Melanoma

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Abstract—*Seventy-nine patients with Stage* III *widely metastatic melanoma were prospectively randomised to a 'no treatment' control group who received on tumour progression DTIC* (250 mg/m^2 i.v. *daily* × 5) *and Actinomycin D* 1.5 mg/m^2 *on Day* 1. *A total of six courses at* 3-week *intervals was given. Chemotherapy was only given on progression of disease. The other group received initially* Corynebacterium parvum (2 mg/m^2) *every* 3 weeks *for a maximum of eight courses and then the same chemotherapy on evidence of progressive disease. Minimum follow up time is* 3 yr. *The chemotherapy response rate (control* 37%, C.parvum 24%) *was not statistically different nor was the effect of chemotherapy on the site of individual metastases. Radiotherapy responses for irradiated soft tissue disease again were not significantly different, between the two patient groups. No significant differences in survival (control group median,* 4 months, *range* 1–46; C.parvum *median* 3 months *range* 1–35) *were observed and only one patient is alive at* 35 months. *The pattern of relapse was also similar in both groups. Reduction in haematological toxicity consequent on chemotherapy was not observed in the* C.parvum-*treated patients. No additional benefit was observed when* C.parvum *was followed by DTIC and Actinomycin D chemotherapy compared with the results from the chemotherapy given alone, although* C.parvum *on this schedule had minimal toxicity.*

INTRODUCTION

CHEMOTHERAPY for widely disseminated, malignant melanoma remains unsatisfactory. The best established single agent, Dacarbazine DTIC produces an average response rate of approx. 20%, [1–3]. Combination chemotherapy has not in general improved the outlook although Dactinomycin has been reported effective both as a single agent and in combination [1–3].

Combined modality treatment, chemoimmunotherapy, was considered a possible avenue of progress and several reports of small patient numbers, using mainly Bacillus Calmette Guerin have been published [1,2,4–7]. However, few randomised studies were reported at the time (1979) the present study was started. *Corynebacterium parvum* was known to have potent immunostimulating properties and some therapeutic effect in both experimental and human tumours [4–6,8].

A randomised study to determine the influence of initial *C.parvum* on a subsequent chemotherapy regimen of DTIC and Dactinomycin was therefore conducted.

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MATERIALS AND METHODS

From April 1979 to June 1982, 79 patients with advanced widely metastatic malignant melanoma were entered into the prospective randomised study. Before treatment, all patients had clinically evident unresectable and evaluable metastatic tumour. Patients older than 75, patients previously treated with chemotherapy and patients with a Karnofsky score of 20 or less were excluded from the study.

Routine haematology, biochemistry, including liver enzymes, chest radiographs and isotope brain, liver and bone scans were performed on study entry to evaluate metastatic disease. Urinary melanogens, serum immunoglobulins and im-

munological evaluation by cutaneous delayed hypersensitivity to three 'recall skin tests' were also performed [8].

The patients were randomised to either immediate *C.parvum* followed by chemotherapy on progression or to a 'watch policy' followed by chemotherapy when progression was evident. Progressive disease was defined as by UICC criteria [9].

There were 39 patients in the chemotherapy group and 40 patients in the *C.parvum* followed by chemotherapy group. Other clinical features are given in Table 1. No significant difference was found between the two treatment groups in relation to the location of primary site, duration of pre-existing lesions, age, sex, Karnofsky score nor between the distribution of sites of metastases given in Tables 2 and 3. Details of the progression of disease in the two patient groups from study entry (at randomisation) to the start of further treatment i.e. chemotherapy, radiotherapy, palliation only is also given in Tables 2 and 3.

Treatment

Corynebacterium parvum, Coparvax (Wellcome Foundation) was given at 2mg/m^2 by i.v. infusion over 3 hr in 300 cc of normal saline, repeated 3-weekly for a total of eight courses or until tumour progression. No routine antipyretics nor steroids were given.

The chemotherapy on progression comprised DTIC 250mg/m^2 i.v. daily for 5 days and Actinomycin D 1.5mg/m^2 on Day 1. *Corynebacterium parvum* was not given concurrently with any chemotherapy course. The treatment was repeated at 3-weekly intervals for a total of eight courses or until further progression. Chemotherapy was delayed by intervals of 1 week until haematological recovery, if the white cell count was less than 4000 or platelet count was 75,000 or less. No dosage reductions were made. Radiotherapy was given when indicated for palliation.

Table 1. *Clinical features*

	Observation → CT	*C.parvum* → CT
Patient Nos.	39	40
Age Median	53 yr	50 yr
Range	23–75	23–73
Sex M : F	15 : 24	22 : 18
Primary site		
Trunk	8	14
Head and neck	5	5
Extremities	21	20
Other	5	1
Duration of primary lesion since 'birth'	16	13
'New lesion' median	12 months (1–144)	24 months (1–552)

No statistically significant differences $P > 0.05$ (chi-square and Mann–Whitney U analysis).

Follow-up

Biochemistry, haematology and chest radiographs were repeated 3-weekly in all patients whilst on treatment or observation. Recall antigen skin tests were repeated at 3 and 6 months. Further investigations were repeated as clinically indicated. After treatment, the patients were seen at 4-weekly intervals for the first 4 months, then 2-monthly intervals for 6 months, then 6-monthly thereafter. Appointments were more frequent when clinically indicated. Standard response criteria were followed [9]. Some patients responded both to chemotherapy and local palliative irradiation, response to chemotherapy was then assessed either before the radiotherapy or in non irradiated areas. No patients have been excluded from analysis due to early death, incomplete treatment etc.

RESULTS

One-hundred-and-twenty-four courses (median 2) of *C.parvum* were given to the 40 patients, 15% of patients received all eight courses and 37% the first course only. No patient satisfied the criteria for response. One hundred and eighteen courses of chemotherapy (median 3) were administered to 32 patients in the 'control group' and 106 courses, median 3, to 29 patients in the *C.parvum* group. The other patients were not considered suitable for chemotherapy due to marked deterioration in performance status (Karnofsky < 30) with the appearance of rapidly accelerating visceral metastatic disease.

Soft tissue, skin, node and brain metastases were irradiated in some patients with stable or progressive disease in these sites (Table 4).

The response in patients who received chemotherapy and radiotherapy is given in Table 4, there were no statistically significant differences between the two patient groups either for patients' response or when separate sites of metastases were analysed. Only one complete chemotherapy response (in the control group) was observed. A further analysis indicated that patients who responded in nonvisceral sites had a significantly higher probability of responding in their visceral metastases as well ($P = 0.0001$ corrected chi-square analysis). No patient who failed to respond in nonvisceral sites demonstrated a response in visceral metastases (see Table 4b).

There was no statistically significant difference in duration of response for the two groups following chemotherapy (Table 4). Following progression after chemotherapy/radiotherapy the intervals to death (median 1 month) in each group were not

Table 2. *Change in metastatic pattern from study entry* (A) *to start of chemotherapy, etc.* (B)

	Observation → CT [39]		*C.parvum* → CT [40]	
	A →	B	A →	B
Local skin	12	15	18	20
Local nodes	6	8	10	11
Distant skin	20	27	26	30
Distant nodes	13	16	12	16
Lung	19	26	17	23
Liver	8	18	6	13
Bone	4	11	3	10
Brain	1	4	1	4
Others: Marrow, spleen, etc.	6	15	5	7

No statistically significant differences between CT alone and *C.parvum* → CT groups

Table 3a. *Change in type of metastases from study entry* (A) *to start of chemotherapy, etc.* (B)

	Observation → CT [39]		*C.parvum* → CT [40]	
	A →	B	A →	B
Nonvisceral	12	5	14	5
Visceral	11	11	7	7
Both	16	23	19	28

$P = 0.54$ chi-square analysis

Number of metastatic sites at start of chemotherapy, etc.

Number of sites	Observation → CT	*C.parvum* → CT
1	20%	27%
2	51%	40%
3	15%	20%
4 or more	14%	13%

$P = 0.76$ chi-square analysis

Table 3b. *Time to progression* (*months*)

	Observation → CT	*C.parvum* → CT
Median	1 month	1 month
Range	< 1–10	< 1–14
	35/39 patients had progressed in ≤ 1 month	27/40 patients had progressed in ≤ 1 month

Table 4a. *Chemotherapy, radiotherapy response*

	Observation → CT		*C.parvum* → CT	
	CT	RT	CT	RT
Progression	14	1	15	6
Static	6	7	7	5
Response	12 (37%)	7 (47%)	7 (24%)	4 (27%)
(Not treated	7	24	11	25)

Chemotherapy $P = 0.54$; radiotherapy $P = 0.09$ chi-square analysis.

Table 4b. *Response and metastatic pattern* (*with duration of response in months*)

Metastatic pattern	'Observation' → CT		*C.parvum* → CT	
	CT	XRT	CT	XRT
Nonviscercal only	3/2 (2,7,4)	4/7 (2,2,6,9)	1/4 (12)	3/10 (2,3,4)
Visceral only	1/11 (4)	–/5 (–)	0/4 (–)	0/3 (–)
Both	8/19 (3,3,4,5,5, 6,7,10)	3/3 (1,2,2)	6/21 (3,4,4,8, 9,12)	1/2 (9)
Duration of response (median range)	4 months (1–10)	2 months (1–9)	7 months (2–12)	3 months (1–9)

NB. Not all metastatic patterns were treated and some patterns were treated with both CT and XRT.

Table 4c. *Sites of response for number of metastatic sites available and treated*

	'Observation → CT'				'C.parvum → CT'			
Site	CT		RT		CT		RT	
Skin	14/34	(41%)	10/14	(71%)	11/41	(27%)	6/18	(33%)
Nodes	8/18	(44%)	4/9	(44%)	5/19	(26%)	1/5	(20%)
Lung	3/21	(14%)	0/0	(–)	0/15	(0%)	0/0	(–)
Liver	0/13	(0%)	0/0	(–)	1/9	(11%)	0/0	(–)
Bone	0/10	(0%)	0/2	(0%)	0/9	(0%)	0/2	(0%)
Brain	0/1	(0%)	1/3	(33%)	0/1	(0%)	0/4	(0%)

No statistically significant difference $P = 0.05$.

significantly different ($P = 0.39$ log rank chi-square). The sites of progressive disease also were similar in the two patient groups (see Table 5).

Toxicity

Of the 124 courses of *C.parvum* given, a pyrexia of 38°C was recorded on 68 and malaise lasting more than 12 hr was noted on 47 occasions. Elevation of hepatic enzymes considered to be due to *C.parvum*, was recorded on 12 occasions. Tachyphylaxis to the malaise and pyrexia was described for 8 out of the 40 patients.

The initial skin test reactivity was not appreciably different for the two patient groups. Interpretation of subsequent differences was confounded by variable numbers of patients available and the influence of chemotherapy. However, an increasing proportion of patients became anergic with time, Table 6. Haematological toxicity grades were analysed for each patient group (only the percentages with grade 3 or more are shown — Table 7). No significant differences ($P > 0.05$) were found for the various grades of toxicity between the two groups. The Karnofsky scores were also analysed for each group, before and after chemotherapy — Table 7 — and no significant differences were found between the two groups. Although there was a larger proportion of the higher and lower scores after chemotherapy in both patient groups.

Table 5. Sites of progression/relapse after chemotherapy and radiotherapy

	Observation → CT	*C.parvum* → CT
Skin	69%	92%
Nodes	38%	40%
Lung	36%	37%
Liver	33%	20%
Bone	21%	25%
Brain	36%	28%
Other	23%	23%

No significant difference between patient groups for sites.
$P > 0.05$ chi-square analysis (chi-square analyses).

Table 6. Changes in skin test reactivity

	On entry		3 months		6 months	
	Observation → CT	*C.parvum* → CT	Observation → CT	*C.parvum* → CT	Observation → CT	*C.parvum* → CT
No. Test positive						
0	63%	55%	69%	63%	73%	82%
1	23%	36%	25%	37%	18%	0%
2	7%	9%	6%	0%	9%	9%
3	7%	0%	0%	0%	0%	9%

Table 7. Haematological toxicity observed (Grade 3 or more)

	Observation → CT		*C.parvum* → CT	
Grade	3	4	3	4
Anaemia	21%	9%	14%	14%
Leucopenia	9%	0%	7%	3%
Thrombocytopenia	12%	9%	–	7%

$P > 0.05$ Fishers exact tests

Toxicity grades — see [9]

Change in Karnofsky performance following chemotherapy

	Before Chemotherapy		After Chemotherapy	
	Observation → CT	*C.parvum* → CT	Observation → CT	*C. parvum* → CT
30	32%	14%	50%	50%
40	32%	33%	6%	17%
50	24%	43%	15%	7%
60	12%	10%	9%	10%
70	–	–	20%	16%
	$P = 0.22$	chi square analyses	$P = 0.90$	

Survival

There was no significant difference in survival between the two patient groups ($P > 0.05$ log rank chi-square analysis) the median values and ranges are given in Table 8. Only one patient is alive (in the *C.parvum* group) at 3 yr. Patients in either group who responded to subsequent treatment survived longer than patients who failed to respond — Table 8 and Figs. 1 and 2.

Table 8. *Survival (median, ranges months)*

	Observation → CT		*C.parvum* → CT	
From study entry	4	(1–46)	3	(1– 35) $P = 0.94$
From primary surgery	42	(1–190)	24	(1–197) $P = 0.11$
Responders*	6	(1–45) $P = 0.002$	6	(3–27) $P = 0.007$
Non-responders*	2	(1–16)	1	(1–96)

*Survival from start of chemotherapy.
Log rank chi square analysis.

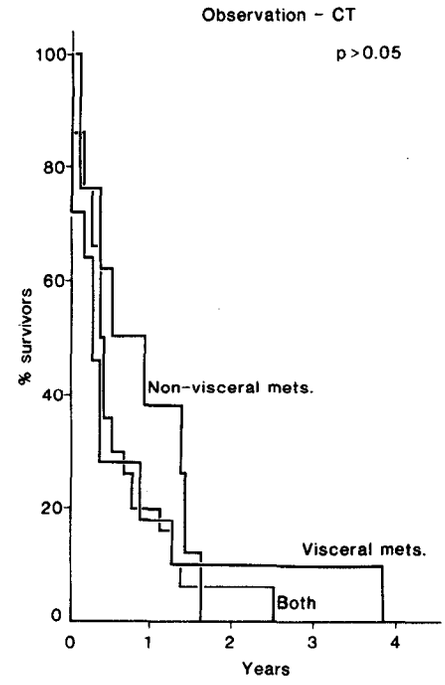

Fig. 1. *Survival and metastatic pattern for observation → CT group*

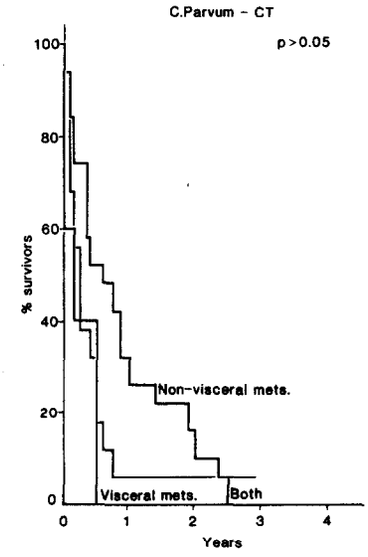

Fig. 2. *Survival and metastatic pattern for* C. parvum → *CT group*

DISCUSSION

The response rates in the present study are similar to the 20–30% values reported by other authors using DTIC and Actinomycin D [1–3,7,10]. A somewhat higher response rate of 37% was recorded in our chemotherapy-alone patient group; there were no obvious clinical differences, e.g. larger proportion of favourable, non-visceral metastases [1–3,7,11] to account for this higher response rate. However, there were slightly more females in the control group and a total of 215 patients would be needed for the observed difference in response rates to be statistically significant.

An earlier study did suggest a greater response rate for a DTIC–BCG treated patient group compared with DTIC alone [12]. Treatment with BCG and chemotherapy also appeared to improve the likelihood of response in visceral metastases [13]. However, in our randomised study no benefit was found in terms of the overall response rate beween the patient groups nor for any difference in sensitivity of particular metastatic sites. An interesting finding from the statistical analysis indicated that the patients who responded in non-visceral sites had a higher probability of responding in visceral metastases. This observation has some importance when response rates in non-visceral metastatic sites are discussed in relation to treatment effects on visceral metastases located in more vital areas.

Corynebacterium parvum was given at a lower dose than usually used by other workers [2,4,6,14,15] and this could explain the slight toxicity although tachyphylaxis was noted in our study. No amelioration of chemotherapy myelosuppression was observed in this study nor in the other study in which consideration was given to this possibility [14].

Although some previous studies, mainly non-randomised, suggested benefit for chemoimmunotherapy over chemotherapy alone for survival, [1–4,6,12] no statistically significant differences were found in the present study either when surviv-

al was taken from date of study entry, date of diagnosis or from the start of chemotherapy. Other randomised studies mainly using BCG have failed to observe any improved survival with immunotherapy [2,4,6]. The use of *C.parvum* and chemotherapy in two other randomised studies also failed to show any obvious benefit from combined modality [14,15]. The response rate in the current study was, however, higher than in a similar study where a 12%, 15% rate was reported using DTIC and Actinomycin D with or without *C.parvum* [14], although the median survival was about double that of our current study.

It is of interest that 15% of patients completed all 6 months of *C.parvum* without obvious increasing disease elsewhere suggesting either a stabilising effect of the *C.parvum* on the disease or an inherent effect unrelated to treatment in these patients, the latter possibility being one reason for the variability in response rate and survivals often quoted [1–7,11].

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