Eur J Cancer Clin Oncol, Vol. 19, No. 1, pp. 49–52, 1983.
Printed in Great Britain.

0277-5379/83/010049-04$03.00/0

VAC (Vincristine, Adriamycin, Cyclophosphamide) Chemotherapy for Metastatic Carcinoma from an Unknown Primary Site

H. ANDERSON,* N. THATCHER, E. RANKIN, J. WAGSTAFF, J. H. SCARFFE and D. CROWTHER
Cancer Research Campaign, Dept. of Medical Oncology, Manchester University and Christie Hospital & Holt Radium Institute, Wilmslow Road, Manchester M20 9BX, U.K.

Abstract—*Twenty patients presenting with metastatic carcinoma from an unknown primary site were studied. All patients were treated with a triple chemotherapy regimen of vincristine, adriamycin and cyclophosphamide repeated at three-week intervals. The response rate was* 50%, *and the four patients achieving complete response are alive and disease-free at* 13, 16, 36 *and* 39 months. *Toxicity was minimal and the majority of patients' performance status improved with the chemotherapy. VAC chemotherapy is indicated for patients with metastases, particularly of soft tissues originating from a carcinoma from an unknown primary site.*

INTRODUCTION

PATIENTS with metastatic carcinoma from an unknown primary site are a problem in clinical oncological management. The number of such patients can account for up to 10% of all referrals to oncological clinics [1, 2]. The need for elaborate and intensive investigation to elucidate the primary site has been the subject of recent study and limited investigation only has been recommended [1, 2]. Intensive investigation is rarely successful in locating the primary tumour site and subsequent patient management is seldom altered [1, 2], although the use of tumour markers is recommended [1, 2] and the recognition of the atypical teratoma syndrome is clearly important [3].

Interest in patients with metastatic carcinoma from an unknown primary has largely been confined to investigational procedures [2]. Very little information on the use of chemotherapy is available, although effective palliation of symptomatic metastases is required [2]. Radiotherapy or other measures may be inappropriate or may have been ineffective and chemotherapy should then be considered [2, 4].

The purpose of the present study of patients with metastases from an unknown primary was to determine the efficacy of a triple chemotherapy regimen given with palliative intent.

MATERIALS AND METHODS

Patient population

Twenty consecutive patients presenting with metastatic carcinoma from an unknown primary site with measurable disease were evaluated. Histological specimens were reviewed by experienced tumour pathologists. The final diagnosis was considered to be anaplastic carcinoma in 13 patients and poorly differentiated adenocarcinoma in the remainder. Autopsy examinations were performed in five patients but failed unequivocally to define the primary site. There were eleven male and nine female patients, the median age being 36 yr. Investigations before chemotherapy included routine haematology, biochemistry, bone marrow aspirate, trephine and chest radiography. All patients had normal values of serum acid phosphatase, α-fetoprotein and β-chorionic gonadotrophin. Eleven patients were found to have elevation of two or more hepatic enzymes. Other investigations including scans were performed as clinically appropriate and to assist treatment evaluation. Clinical features of the patients including the sites of metastases are given in Table 1. All patients had metastatic disease in more than one organ system

Accepted 11 August 1982.
*To whom requests for reprints should be addressed.

or at differing anatomical sites. The interval from diagnosis to start of chemotherapy was one month or less for 10 patients, 1–2 months for three patients and more than two months for the remaining patients. No patient had been given previous chemotherapy. Three patients had received palliative radiotherapy before the chemotherapy regimen was started.

Chemotherapy regimen

All patients were treated with the following 'VAC' combination: vincristine 1.4 mg/m^2, adriamycin 50 mg/m^2 and cyclophosphamide 500 mg/m^2, given by i.v. bolus injection. Chemotherapy courses were repeated at three-week intervals and discontinued if disease progression occurred, after 10 courses in patients who had responded, or at adriamycin cardiac tolerance (550 mg/m^2).

Evaluation

The criteria for evaluation of response were as follows: complete response (CR): complete disappearance of all objective evidence of tumour for a month or more; partial response (PR): decrease of 50% or more of one diameter of measurable disease for at least four weeks without progression elsewhere; no response (NR): no significant change for at least one month, including stable disease, and progressive disease, i.e. appearance of new lesions or estimated increases of 25% or more in existing lesions.

The duration of response was taken as the interval from the first record of response to the date of first observation of progressive disease. Survival was taken from the date of the first injection of chemotherapy. The Karnofsky performance score was recorded immediately before the first chemotherapy course and again after the last course.

Toxicity assessment

Acute and subacute toxicity, including haematological; gastrointestinal side-effects were noted and graded according to Miller *et al.* [5].

RESULTS

An objective response was observed in ten (50%) patients, with a complete response rate of 20% (Table 1). Lymph node metastases and soft tissue disease responded best, but partial responses were also noted in visceral (lung, liver) sites (Table 1). The majority of patients (8) responded within six weeks of starting chemotherapy, i.e. after the first treatment course. Only one patient responded later than nine weeks, after the fourth course of chemotherapy. The duration of response is given in Table 2 (median value 9 months, range 1–39 months). All the complete responders are alive, in complete remission.

The change in the Karnofsky Performance Score following chemotherapy is displayed in Table 3. There was an improvement in the score with treatment: the median value was 50 (range 30–80) before chemotherapy and 70 (range 0–100) one month after the final course. The total number of chemotherapy courses given was 99;

Table 1. Metastatic sites and response to chemotherapy

Patient No.	Response status	Sites of metastases					
		Skin	Lung	Liver	Bone	Nodes	Other
1	PR	(x)	(x)	—	—	(1)	—
2	NR	—	—	—	x	—	Bone marrow
3	NR	—	—	—	—	1	—
4	CR	—	—	—	—	(2)	(ST, abdomen)
5	CR	—	—	—	—	(1)	(ST, pelvis)
6	PR	—	—	—	—	(1)	(ST, abdomen)
7	PR	—	(x)	—	—	(3)	(Pleura)
8	CR	—	—	—	—	(1)	(Bone marrow)
9	NR	—	—	x	x	—	—
10	NR	x	x	—	—	3	ST, orbit
11	NR	—	—	—	—	2	ST, abdomen
12	NR	—	—	x	x	3	—
13	NR	—	x	—	—	3	—
14	PR	—	—	—	x	(3)	—
15	NR	—	—	—	—	1	ST, abdomen
16	NR	x	x	—	—	3	—
17	CR	—	—	—	—	(1)	—
18	PR	—	—	(x)	—	(1)	—
19	PR	—	—	(x)	—	(2)	—
20	NR	—	x	—	—	3	—

NR, no response: PR, partial response; CR, complete response; ST, soft tissue; 1, above and below diaphragm; 2, below diaphragm; 3, above diaphragm; ( ), site of response.

Table 2. Response duration (months) *and patient status*

Patient No.	Response status	Response duration	Status
1	PR	1	Dead
4	CR	39	Alive n.e.t.
5	CR	16	Alive n.e.t.
6	PR	2	Dead
7	PR	26	Alive, relapse
8	CR	13	Alive n.e.t.
14	PR	5	Dead
17	CR	36	Alive, n.e.t.
18	PR	2	Alive
19	PR	2	Alive

PR, partial response; CR, complete remission; n.e.t., no evidence of tumour.

Table 3. Change in patients' Karnofsky score with chemotherapy

KP Score	Before treatment	After last treatment
<40	5	6
50	8	1
60, 70	6	4
80	1	5
90, 100	-	4

three patients received one or two courses of chemotherapy, nine patients 3–6 courses and eight patients 6 or more courses. The haematological toxicity was slight: leucopenia, (less than 3.9×10^3 cells/mm^3) was observed in eight patients and thrombocytopenia (less than 75×10^3 cells/mm^3) in three patients. Only two patients required blood transfusion and one patient required intravenous antibiotics, although another six patients were prescribed antibiotics for presumed infection.

Chemotherapy was delayed in two patients to allow bone marrow recovery. All patients experienced nausea and the majority (13 patients) transient vomiting. Other side-effects included some alopecia in all patients, intestinal colic in one patient, parasthesiae in three patients, and cystitis and transient diarrhoea (for less than two days) in a further three patients.

The median survival of the total patient group was eight months, range 2 weeks–48 months (Fig. 1). There were no statistically significant differences ($P > 0.05$) in survival between responders and non-responders, nor between patients with normal and elevated hepatic enzyme values.

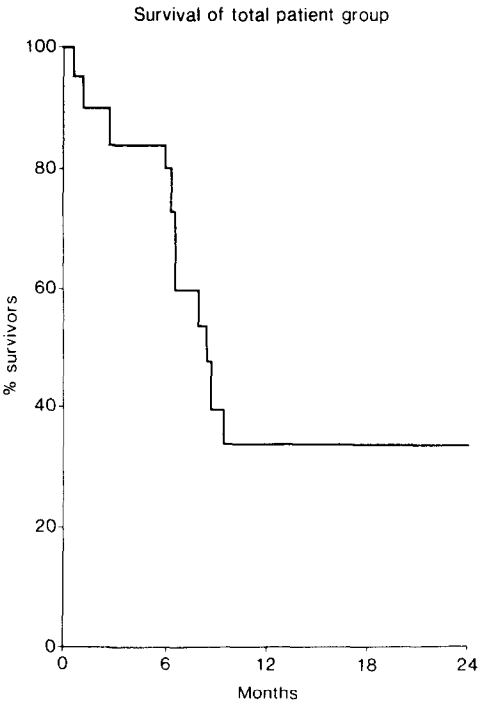

Fig. 1. Survival of total patient group.

DISCUSSION

Triple agent chemotherapy with the 'VAC' regimen gave a 50% response rate in the study group. There are few reports of other regimens, although response rates of 5–36% have been recorded in a recent review [2]. A randomised study by Woods *et al.* [4] demonstrated the superiority of adriamycin with mitomycin C (36% response rate) over a triple chemotherapy with cyclophosphamide methotrexate and 5FU. Clearly the patient characteristics are important and the present study indicated the value of VAC treatment for a minority of patients (20%) who are alive and continue in complete remission.

The regimen was not associated with severe side-effects and good palliation with an improvement in the patients' performance was noted. The VAC chemotherapy is therefore useful for patients with metastases, particularly of skin, nodes and soft tissues from a carcinoma of unknown primary site.

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