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Is Ectopic Production of Human Chorionic Gonadotrophin (hCG) or Alpha Fetoprotein (AFP) by Tumours a Marker of Chemosensitivity?

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Abstract—*We have treated eight patients with various tumours producng hCG or AFP with the high risk gestational choriocarcinoma regimen EMA/CO. Marker response was seen in two of three tumours producing AFP and in all of five tumours producing hCG. Three further patients were treated with EpPt/OMB, a regimen used in relapsed germ cell tumours. All responded biochemically. All complete biochemical responses were accompanied by anatomical response. These responses may reflect particular sensitivity in the marker producing tumours and marker measurements would identify this subgroup. These findings do not preclude the possibility that these cytotoxic regimens may have activity against a wide range of solid tumours.*

INTRODUCTION

PRODUCTION of human chorionic gonadotrophin (hCG) and alpha fetoprotein (AFP) is characteristic of a high proportion of germ cell tumours and hCG is an invaluable marker of gestational trophoblastic tumours. Both these groups of tumours are usually curable by chemotherapy and in both cases the markers are useful in monitoring the progress of individual patients. Tumours originating from somatic cell lines may also produce these substances [1]. There are reports of patients with common solid tumours who have had high levels of hCG and who have enjoyed good responses to chemotherapy which was guided by the serum hCG level [2, 3]. The use of placental hormones to monitor disease has been described by Muggia *et al.* in four patients who responded to chemo- and radiotherapy [4].

A patient (Case 1) presented to this hospital with a cerebral metastasis from what was believed to be gestational choriocarcinoma because of the initial histological differential diagnosis and the serum hCG level. This diagnosis was not sustained on further investigation, which showed that the tumour was a gastric adenocarcinoma with trophoblastic differentiation. Nevertheless, in view of the excellent response to the choriocarcinoma regimen she was receiving this was continued.

This paper is a report of a consecutive series of subsequent patients at Charing Cross Hospital with elevated serum hCG or AFP associated with epithelial tumours who have been treated with chemotherapy regimens used for gestational trophoblastic tumours or germ cell tumours. A further patient treated at the same time in the Royal Lancaster Infirmary is also reported.

PATIENTS AND METHODS

Eight patients were treated with the EMA/CO regimen (Table 1) which is used in this hospital for treatment of patients with gestational choriocarcinoma at high risk of developing drug resistance [5].

Three further patients were treated with platinum based chemotherapy (EP/OMB, Table 1). This was because of the initial possibility that they had germ cell tumours. This was subsequently rejected in each case on histopathological grounds. Both treatments continued until the marker concentrations had been normal for 3 months or the tumour progressed. One patient was treated for carcinoma of the bladder at the Royal Lancaster Infirmary using bleomycin, etoposide and cisplatin (BEP) [6].

Radioimmunoassays were used for marker measurements. That for hCG employs an antibody specific for the beta subunit, the sensitivity is 2 IU/l and the upper limit of normal is 5 IU/l. The

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Table 1. Chemotherapeutic regimens used

EMA/CO	
Day 1	Etoposide 100 mg/m^2 Actinomycin D 0.5 mg Methotrexate 100 mg/m^2 bolus followed by 200 mg/m^2 infusion over 12 hr (patients with brain metastases receive 1000 mg/m^2 over 24 hr)
Day 2	Etoposide 100 mg/m^2 Actinomycin D 0.5 mg Folinic acid rescue
5-day drug-free interval.	
Day 8	Vincristine 1 mg/m^2 Cyclophosphamide 600 mg/m^2
Sequence repeated after 6-day drug-free interval.	
EpPt/OMB	
Day 1	Etoposide 100 mg/m^2 Cisplatin 100 mg/m^2 over 12 hr with hydration, magnesium supplements and mannitol.
7-day drug-free interval.	
Day 9	Vincristine 1 mg/m^2 Methotrexate 100 mg/m^2 bolus followed by 200 mg/m^2 infusion over 12 hr.
Day 10 and 11	Bleomycin 15 mg/24 hr infusion Folinic acid rescue
Sequence repeated after 7-day drug-free interval.	
Folinic acid rescue = folinic acid 15 mg 12 hourly × 4 doses starting 24 hr after methotrexate starts, dose and duration increased if methotrexate toxicity likely.	

sensitivity of the AFP assay is 2 kU/l, the upper limit of normal is 10 kU/l. The frequency of raised serum concentrations of these substances in patients with various epithelial malignancies was determined from the computer-based records of the supraregional assay service laboratory at Charing Cross Hospital.

Table 2. Occurrence of elevated hCG and AFP levels in Charing Cross Hospital laboratory

	hCG			AFP		
Primary site	raised	*n*	%	raised	*n*	%
Stomach	4	32	12.5	9	46	19.6
Pancreas	5	14	35.7	1	23	4.3
Oesophagus	0	4	0	2	6	33.3
Lung/bronchus	9	97	9.3	7	106	6.7
Bladder	6	32	18.8	3	23	13

n = number of patients on whom marker requested.

A biochemical complete response (CR) is defined as return of the serum concentration of the marker to normal. A partial response (PR) is reduction of the level to less than 1/10 of its initial value, a minor response (MR) is reduction of the level to less than half its initial value.

Anatomical CR is complete resolution of all assessable lesions. PR is reduction of the size of such lesions by 50%.

RESULTS

Table 2 shows the frequency of raised levels of hCG and AFP in patients with the same diagnoses as those described here.

The biochemical responses are recorded in Table 3. The hCG level fell substantially in all

Table 3. Tumour sites and biochemical responses

	hCG			AFP		
Case No.	Initial	Nadir	Response	Initial	Nadir	Response
Carcinoma of stomach treated with EMA/CO						
1	17280	<1	CR			
2				5317	18	PR
3	12	2	CR			
4				1875		no response
Carcinoma of pancreas EMA/CO						
5	14660	5166	MR			
6	26	<1	CR			
Carcinoma of oesophagus EMA/CO						
7				16730	2904	MR
Carcinoma of small bowel EMA/CO						
8	929	3	CR			
Carcinoma of bronchus EpPt/OMB						
9	23	<1	CR			
10	7270	6	PR	21	<1	CR
Carcinoma of bladder EpPt/OMB						
11	3609	<2	CR	59	<2	CR
Carcinoma of bladder BEP [6]						
12	68600	2	CR			

eight patients in whom it was raised, six patients achieved CR; the AFP level fell in four out of five patients, two of whom achieved CR. The duration of response has been variable; in patients with carcinomas of stomach and bronchus it has been of short duration (Fig. 1), the maximum was 4 months. The patient with small bowel carcinoma had a 3 month biochemical remission. One patient with carcinoma of the bladder (Fig. 2) has remained disease-free 12 months after the end of treatment.

Assessable lesions responded in all patients with stomach carcinoma. Investigation by computed tomography and ultrasound at the end of treatment showed minimal residual disease. The results in the other patients are listed in Table 4. The objective response rate was 7/10 excluding case 5 (early death) and case 8 (not assessable).

The difficulties of using treatment of this intensity are illustrated by case 7, a 62-year-old man with carcinoma of the oesophagus. He had a good initial biochemical response (Fig. 3) but having developed nausea and vomiting following a course of chemotherapy he neglected medical advice. He became dehydrated and developed renal failure, leucopenia and mucositis. It was therefore impossible to maintain the planned tempo of drug administration. Barium swallow showed no change in the lesion, although he had noticed improvement in his dysphagia.

The median survival of this heterogeneous group of patients was 292 days from the date of referral.

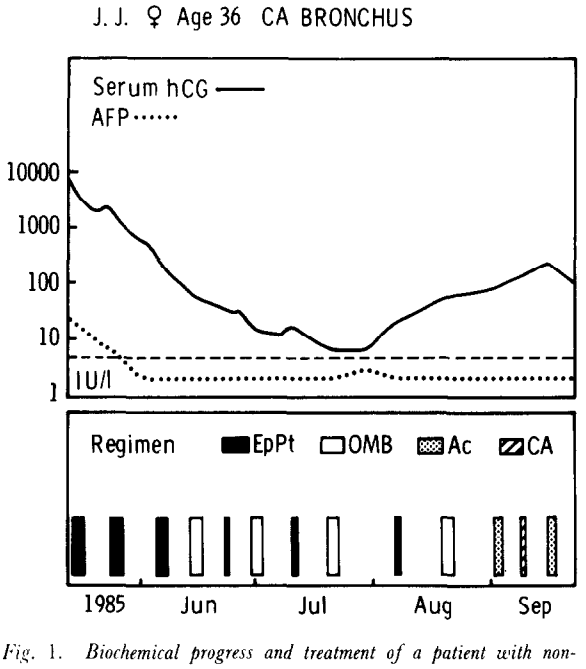

Fig. 1. Biochemical progress and treatment of a patient with non-small-cell carcinoma of the bronchus. (Ac = actinomycin D 0.5 mg IV 2 days, CA = cyclophosphamide 400 mg/m² + adriamycin 20 mg/m²).

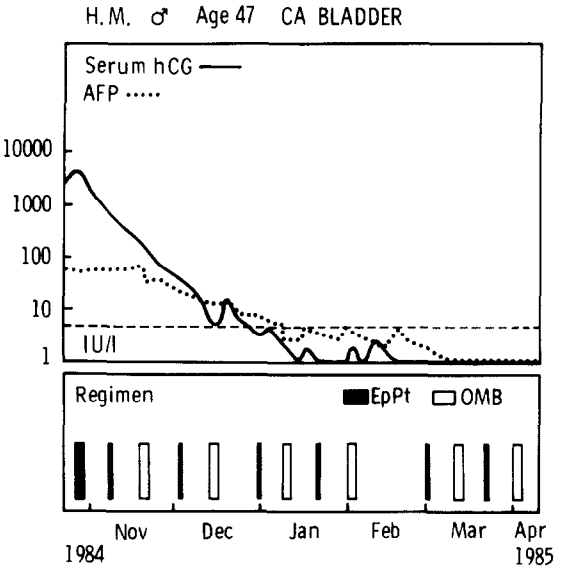

Fig. 2. Biochemical progress and treatment of a patient with carcinoma of the bladder resulting in complete response.

DISCUSSION

Trophoblastic tumours of gestational or germ cell origin are among the most amenable to treatment with chemotherapy. The initial successful use of methotrexate in both groups, summarised in 1959 by Brucker [7], led on to the present combination regimens which have proved successful in achieving the current long term survival figures of 93% for high risk gestational trophoblastic disease [5] and 92% for metastatic germ cell tumours of gonadal or extragonadal origin [8]. In contrast, chemotherapy for the range of tumours described here has proved much less successful. The best response rates in carcinoma of the stomach or pancreas are in the range 48–55%, using the FAM schedule (5-fluorouracil, Adriamycin (doxorubicin) and mitomycin C) or its derivatives [9]. Those for carcinoma of the oesophagus and non-small-cell carcinoma of the bronchus are much less than these. The best response rate for carcinoma of the bladder is 68% [9].

It is possible that the patients reported here were misdiagnosed cases of germ cell or gestational trophoblastic tumours. This is unlikely because the histological material was assessed by pathologists who are experienced in both conditions. In addition, the responses we have seen were not associated with long-term remission which would be expected in such cases, indeed it is possible that some of the few patients whose treatment for gestational choriocarcinoma is unsuccessful in fact have hCG producing epithelial tumours. A malignant trophoblastic tumour arising from a transitional cell carcinoma of the bladder has been described [10].

Table 4. Anatomical response and outcome

Case	Anatomical Response	Outcome
1	PR 4 months	Died of drug resistant disease
2	PR 1 month	Died of drug resistant disease
3	PR 2 months	Died of drug resistant disease
4	None	Alive with disease
5	Early death	Died after one course
6	None	Responded to radiotherapy; alive with relapse at 11 months
7	Symptomatic	Chemotherapy curtailed by toxicity (Fig. 3)
8	Not assessable	Alive with disease at 24 months hCG normal for 3 months
9	PR	Lost to followup at 4 months
10	PR	Alive, second biochemical response (Fig. 1)
11	CR	Alive and tumour free at 12 months (Fig. 2)
12	CR	Died in renal failure at 11 weeks. No residual disease at necropsy.

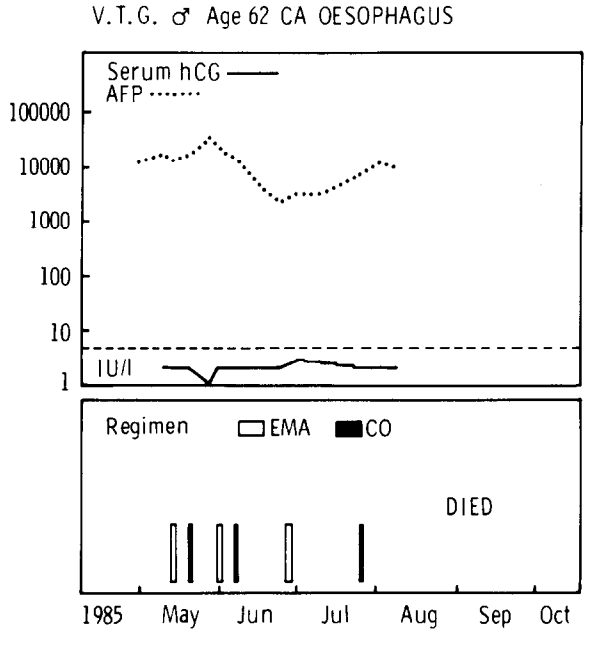

Fig. 3. Biochemical progress and treatment of a patient who died from carcinoma of the oesophagus having failed to receive the planned chemotherapy because of toxicity.

The production of markers characteristic of trophoblast or yolk sac tissue by somatic tumours is well documented. The recent finding that genes for tumour markers are clustered near cellular oncogenes [11] offers a possible explanation for the observed concordance between marker production and chemosensitivity. The occurrence of responses to chemotherapy in marker producing tumours has been described in colon and lung tumours [2, 3]. Dennis and Turner [10] report a case of choriocarcinoma of the bladder which did not regress with chemotherapy, although they do not report serial hCG levels.

The high response rate in this group of patients may be attributable to a number of factors. Those tumours which produce markers may have enhanced sensitivity to cytotoxic drugs in general or they may be sensitive to particular cytotoxic drugs [5, 6, 8]. Alternatively, the response rate may be a result of the intensity of chemotherapy which has been administered being greater than that of the standard FAM [9]. In order to examine these possibilities we are using the EMA/CO schedule prospectively in a pilot study in patients with upper gastrointestinal tumours irrespective of marker production. The use of intensive chemotherapy in this group of patients outside a clinical trial conducted in a cancer treatment centre cannot at present be advocated because of the potential hazards of such treatment, which are increased in older people.

The overall anatomical response rate that we have observed is at least as good as may be expected in these tumours. However, the effect of chemotherapy on the marker levels, with responses in all tumours producing hCG and in four out of five producing AFP, suggests that the elements of the tumour which produce them are particularly sensitive.

It is important that serum hCG and AFP should be evaluated as prognostic indicators in clinical trials in all common epithelial tumours. It may be that patients with elevated serum concentrations of these substances will benefit from chemotherapy active in gestational or germ cell tumours.

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