Cancer Immunol Immunother (1991) 33: 403–410
034070049100084H

Cancer Immunology Immunotherapy

Prospective assessment of the role of five tumour markers in breast cancer

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Received 20 November 1990/Accepted 7 March 1991

Summary. Retrospective analysis previously identified significant elevation of five tumour markers, carcinoembryonic antigen (CEA), ferritin, orosomucoid, *C*-reactive protein and erythrocyte sedimentation rate (ESR), in patients with systemic breast cancer and showed that changes in each of these markers individually correlated significantly with therapeutic response. In this study we have prospectively tested these findings. None of the five markers was significantly elevated in primary breast cancer compared to normal control or benign breast disease groups. They therefore appear to have no role either in screening or in the differential diagnosis of breast cancer. There was a significant elevation of all five markers in patients with systemic breast cancer ($P < 0.0001$; analysis of variance) but sequential changes in CEA and ESR only correlated significantly with the UICC-assessed response. Prospective confirmation of the correlation between changes in serum CEA and ESR provides the basis for using these markers in the assessment of response to therapy in patients with systemic breast cancer.

Key words: Breast cancer – Tumour markers – Therapeutic response

Introduction

Numerous studies with retrospective analysis have reported on the apparent usefulness of tumour markers in breast cancer. The value of such retrospective studies is limited particularly since few of these initial reports have subsequently been confirmed in prospective studies. We have recently reported on the use of five tumour markers in breast cancer; these were serum carcinoembryonic antigen (CEA), ferritin (FERR), C-reactive protein (CRP), orosomucoid (ORO) and erythrocyte sedimentation rate (ESR). All five markers were elevated in patients with metastatic disease and changes in the concentration of each of these markers individually correlated with response to systemic therapy assessed by UICC criteria [43]. In this study we have prospectively tested the place of these five markers (serum CEA, FERR, CRP, ORO and ESR).

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Patients and methods

The five serum markers were measured in five groups of patients.

Systemic breast cancer. Over a 12-month period 85 consecutive patients with newly diagnosed metastatic breast cancer presented to our unit. The site of initial metastatic disease was bone ($n = 33$), lung ($n = 27$), bone and lung ($n = 11$) and viscera ($n = 14$). No patient had received adjuvant systemic therapy. All 85 patients received systemic endocrine therapy as the initial treatment; 14 premenopausal patients received the luteinising-hormone-releasing hormone agonist goserelin, Zoladex (ICI Pharmaceuticals, UK) 3.6 mg monthly by subcutaneous injection and the anti-oestrogen tamoxifen, Nolvadex (ICI Pharmaceuticals, UK) 20 mg twice daily. Post-menopausal patients were treated either with tamoxifen 20 mg twice daily ($n = 69$) or the synthetic progestagen megestrol acetate, Megace (Bristol Myers, UK) 160 mg twice daily ($n = 2$).

Patients were assessed before treatment and at 2-monthly intervals by the International Union Against Cancer (UICC) criteria [15] and by tumour markers. It is conventional when assessing response in advanced breast cancer to exclude from the analysis of response patients with a life expectancy of less than 3 months at presentation and patients with systemic disease unassessable by UICC criteria. Direct comparison between changes in tumour marker concentrations and UICC assessed response has therefore been made in patients who survived for more than 3 months ($n = 65$).

Locally advanced primary breast cancer. Sixty consecutive patients with histologically confirmed locally advanced primary breast cancer (i.e. clinically tumour >5 cm maximum diameter) were entered into this study. Since the 5-year survival of patients with locally advanced disease is 25%–30% the majority must have covert metastases at initial presentation. Patients were regarded as having locally advanced disease only if clinical examination and X-rays of the chest and pelvis did not detect metastases. All patients had serum marker concentrations measured at diagnosis prior to any therapy.

Primary operable breast cancer. One hundred consecutive patients with histologically confirmed primary operable breast cancer (clinically stage I and II) had serum marker concentrations measured prior to surgery.

Benign breast disease. Pre-surgery blood samples were obtained from 100 consecutive women presenting with benign breast disease confirmed by excision biopsy and histology.

Normal controls. A group of 56 women with no evidence of breast disease formed a normal control group; 25 were either normal healthy women or were patients with benign conditions admitted to hospital for minor surgical procedures; all had no history of breast disease and normal breasts on clinical examination. Blood samples were also obtained from the remaining 31 women who attended one session of the breast screening programme in Nottingham; all 31 women had no history of breast problems and no mammographic evidence of breast disase.

The mean ages (± SD)(years) for each of the five groups of patients were as follows: normal controls 48.8 (±14.1), benign breast disease 43.1 (±12.1), stage I/II breast cancer 52.9 (±8.9), stage III breast cancer 63.4 (±11.5) and systemic breast cancer 60.5 (±12.2) years. These results were significantly different on analysis of variance (P <0.0001). There was no significant difference in mean age between patients with stage III and systemic breast cancer: both of these groups were significantly older than normal subjects, patients with benign breast disease and patients with stage I/II breast cancer. Of the last three groups, patients with stage I/II breast cancer were significantly older than patients with benign breast disease.

Patients with non-malignant disease (i.e. normal controls and benign breast disease groups (n = 156) were divided into two groups, above and below 60 years [mean 41.8 (±10.8) and 65.1 (±5.4) years], to establish if the serum concentrations of these markers were age-related. There was no significant difference between the two groups for any of the five markers: mean(± SD) CEA values were 2.0 (±1.9) and 1.9 (±1.2) ng/ml, ESR 11.8 (±7.3) and 10.2 (±6.0) mm/h, FERR 53.4 (±32.5) and 77.7 (±35.8) ng/ml, ORO 0.86 (±0.23) and 1.15 (±0.96) g/l and CRP 5.0 (±0.0) and 6.28 (±2.7) mg/l.

Clinical assessment of response. Patients with metastatic breast cancer were assessed by UICC criteria prior to commencing anticancer therapy and after 2,4 and 6 months therapy or between these times if clinically indicated. To qualify for complete (CR) or partial (PR) response or static disease (SD) (no change) the minimum duration taken was 6 months as recommended by the British Breast Group [2]. Assessment of response in all patients was externally reviewed.

Survival of patients with PR or SD for at least 6 months is similar, both groups surviving significantly longer than patients with progressive disease by 6 months [18, 30]. In analysing the correlation between biochemical marker movement after 2, 4 or 6 months therapy and the UICC-assessed response we combined the categories of CR, PR and SD into a "non-progressive" disease group and compared this with the group of patients showing progression.

Biochemical assessment of response. Biochemical response to therapy in patients with metastatic breast cancer is assessed in the same manner for all tumor markers studied in this unit, i.e. any change in marker while the patient is on therapy is related to the pre-treatment baseline value of the marker and the interassay coefficient of variation (CV) of the marker (<10% for all five markers in this study). A cut-off level for each individual marker of the mean ±2 SD of the normal control group was calculated. Patients who never showed an elevation of the marker above this level were regarded as biochemically unassessable for that particular marker. Patients who started with an initially elevated value, which fell to below the cut-off level, or patients with an initial value above the cut-off level, which subsequently decreased by more than the interassay CV (10%) for that particular marker were regarded as showing a decreasing marker level indicative of "biochemical response": as in our retrospective study [43] CEA was scored –2 and the other markers were scored –1. Patients with an initial pretreatment value below the cut-off level, which subsequently rose above the cut-off level, or patients with an initial value above the cut-off level, which subsequently increased above the interassay CV (10%) for that particular marker, were regarded as showing an increasing marker level indicative of "biochemical progression" (all markers scored +2). Patients with levels that started and remained above the cut-off but moved by less than the interassay CV (10%) were regarded as "biochemically stable" and scored +1.

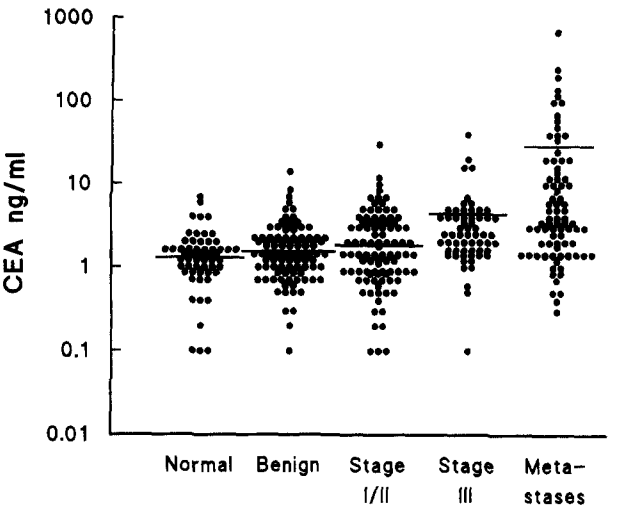

Fig. 1. Serum carcinoembryonic antigen (*CEA*) in controls and in breast cancer patients. ———, Mean value for each group; analysis of variance: P <0.0001; Scheffe test: only metastases group significantly elevated from normal, benign, stage I/II and stage III groups

Statistical analyses. Data were analysed using the statistical package SPSSX-21 [31]. Analysis of variance and Scheffe range testing were used to compare marker values for stage of disease. χ^2 analysis with Yates correction where appropriate and Fisher's Exact test were used to compare frequencies of integers between two variables. In accordance with convention in all analyses P <0.05 was taken as significant.

Serum markers. Venous blood was withdrawn, allowed to clot and centrifuged and serum was removed and divided into aliquots before being stored initially at –20° C and subsequently transferred to storage at –70° C. All samples were assayed blind of clinical information on aliquots thawed once only Marker concentrations in each specimen were always measured in duplicate.

Carcinoembryonic antigen (CEA). CEA was measured in aliquots of serum using the commercially available CIS ELSA kit (CIS, High Wycombe, UK). The intra- and inter-assay coefficients of variation (CV) were 6.9% and 7.1% respectively.

Ferritin (FERR). Serum FERR was measured in sample aliquots using the commercially available CIS ferritin radioimmunoassay kit (CIS, UK). Intra-assay variation was estimated at three different concentrations and inter-assay variation at two different concentrations. The intra-assay CV varied between 4.58% and 7.75%. The inter-assay CV ranged from 10.4% to 10.5%.

Orosomucoid (ORO). Orosomucoid (α-1 acid glycoprotein) was measured by immuno-tubimetry as previously described [43]. The inter-assay CV varied from 5.83% to 5.97%.

C-reactive protein (CRP). CRP assay was measured by a latex-enhanced immunoassay in a centrifugal fast analyser as previously reported [43]. The inter-asay CV ranged from 4% to 4.4%.

Erythrocyte sedimentation rate (ESR). Samples of 2 ml freshly aspirated blood were placed in a tube containing EDTA. ESR was measured by the Westergen technique.

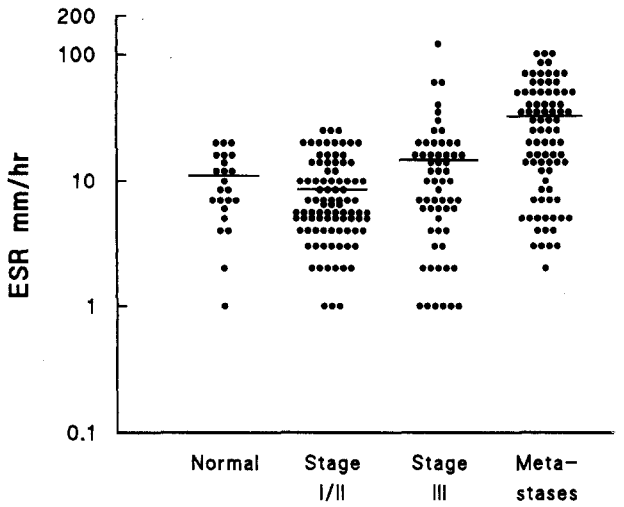

Fig. 2. Erythrocyte sedimentation rate (*ESR*) in controls and in breast cancer patients. ———, Mean value for each group; analysis of variance: $P < 0.0001$; Scheffe test: only metastases group significantly elevated from normal. stage I/II and stage III groups

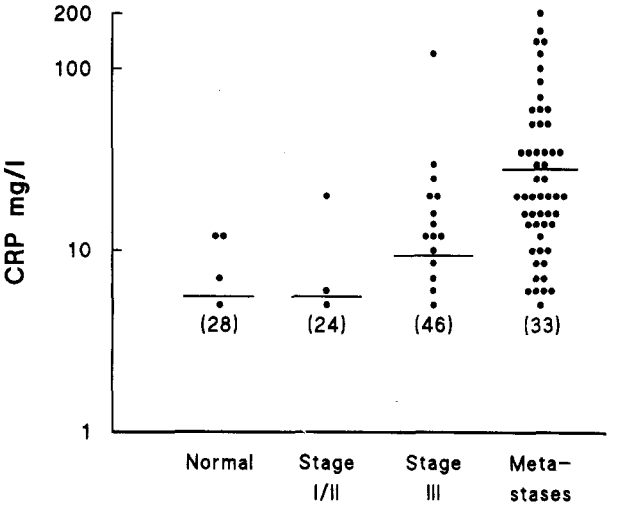

Fig. 3. Serum C-reactive protein (*CRP*) in controls and in breast cancer patients. *Numbers in parentheses* represent number of patients with CRP levels at lower limit of assay (i.e., 5 mg/l). Mean value for each group shown by ———; analysis of variance: $P < 0.0001$; Scheffe test: only metastases group significantly elevated from normal, stage I/II and stage III groups

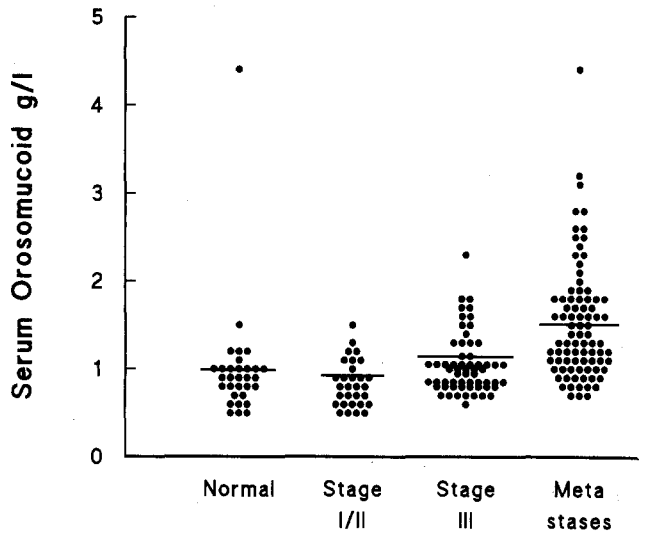

Fig. 4. Serum orosomucoid (*ORO*) in controls and in breast cancer patients. ———, Mean value for each group; analysis of variance: $P < 0.0001$; Scheffe test: only metastases group significantly elevated from normal, stage I/II and stage III groups

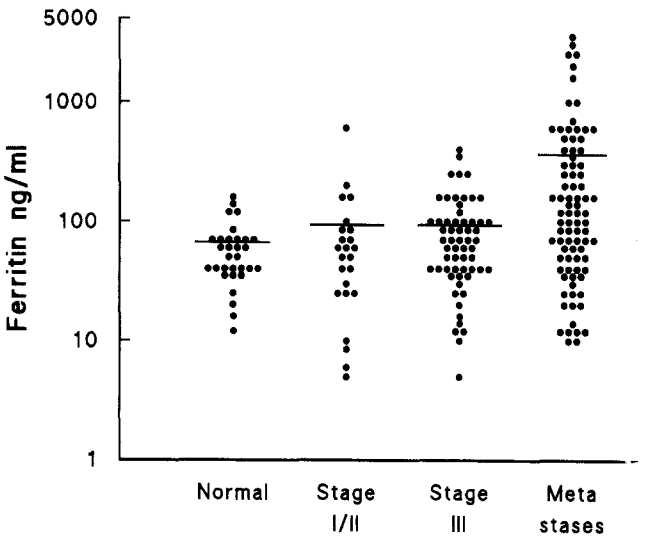

Fig. 5. Serum ferritin (*FERR*) in controls and in breast cancer patients. ———, Mean value for each group; analysis of variance; $P = 0.0002$; Scheffe test: only metastases group significantly elevated from normal, stage I/II and stage III groups

Results

Elevation of markers in breast cancer patients

Scatterplots of each of the five markers for the five patient groups are shown in Fig. 1–5. All five markers were significantly raised on analysis of variance; $P = 0.0002$ for FERR and $p < 0.0001$ for the other four markers. Multiple-range testing between the groups was carried out using the Scheffe test. Patients with systemic breast cancer showed a highly significant elevation over all other groups for each of the five markers. There was no significant difference between any of the other patient groups for any of the five markers.

The markers were further examined to establish the percentage of patients in each group with elevated levels of each individual marker or of any one of the five markers. The concentrations reported in our previous study as indicating systemic disease, based on the mean +2 SD of the control group, were used; i.e. CEA 6 ng/ml, ESR 20 mm/h, CRP 10 mg/l, ORO 1.2 g/l and FERR 200 ng/ml [43]. The corresponding levels (mean +2 SD) for the group of normal women in this study were CEA 5 ng/ml, ESR 24 mm/h, CRP 9.4 mg/l, ORO 2.3 g/l and FERR 135.3 ng/ml. For CEA the means +2 SD level for the normal and benign breast groups combined in this study was 5.6 ng/ml.

Table 1. The number of patients (%) in each group showing marker elevation above predefined normal ranges (mean ±2 SD)

Markers[a]	Non-malignant (NM)	Number of patients (%) in each group			Systemic disease
		Stage I/II	Stage III	Non-systemic (NM+I/II+III)	
CEA (ng/ml)					
≤ 6	150 (96.2)	91 (91)	53 (88.3)	294 (93)	52 (61.2)
> 6	6 (3.8)	9 (9)	7 (11.7)	22 (7)	33 (38.8)
ESR (mm/h)					
≤ 20	21 (91.3)	80 (88)	47 (78.3)	148 (85)	36 (43.4)
> 20	2 (8.7)	11 (12)	13 (21.7)	26 (15)	47 (56.6)
CRP (mg/l)					
≤ 10	29 (93.5)	25 (96)	50 (83.3)	104 (88.9)	42 (49.4)
> 10	2 (6.5)	1 (4)	10 (16.7)	13 (11.1)	43 (50.6)
ORO (g/l)					
≤ 1.2	29 (93.5)	28 (93)	46 (76.7)	103 (85.1)	37 (43.5)
> 1.2	2 (6.5)	2 (7)	14 (23.3)	18 (14.9)	48 (56.5)
FERR (ng/ml)					
≤200	31 (100)	22 (92)	55 (91.7)	108 (93.9)	54 (63.5)
>200	0	2 (8)	5 (8.3)	7 (6.1)	31 (36.5)
Five markers combined					
No marker elevated	145 (92.9)	79 (79)	32 (53.3)	256 (81)	16 (18.8)
≥1 marker elevated	11 (7.1)	21 (21)	28 (46.7)	60 (19)	69 (81.2)

	Systemic (vs non-malignant)	Systemic (vs non-systemic)
Sensitivity (%)	81.2	81.2
Specificity (%)	93.0	81.0
Predictive value of abnormal test (%)	97.1	53.5
Predictive value of normal test (%)	90.1	94.1

[a] CEA, carcinoembryonic antigen; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; ORO, orosomucoid; FERR, ferritin

To calculate the overall false positive rate for patients with non-malignant conditions those in the normal and benign breast disease groups were combined into one non-malignant (NM) group. The results shown in Table 1 divide patients into the following groups: non-malignant (NM), stage I/II, stage III, non-systemic breast cancer (NM + stage I/II + stage III) and systemic breast cancer. Using the levels suggested by our previous retrospective study [43] the sensitivity of individual markers for systemic breast cancer ranged from 36.5% to 56.6%. However, when all five markers were considered, the sensitivity for systemic disease of any one of the five markers being elevated was 81.2% with a specificity for non-malignant disease and non-systemic breast cancer of 92.9% and 81% respectively.

Decreasing the cut-off level to the mean +1 SD of the normal controls increased the sensitivity for systemic disease of any one marker being elevated to 86%, while specificity for non-malignant disease and non-systemic breast cancer decreased to 87% and 70% respectively. Increasing the cut-off level to the mean +3 SD of the normal controls decreased sensitivity to 73% and increased specificity to 99% and 93% respectively.

Table 2. Mean pretreatment serum concentration (± SD) by site of initial metastases

Marker	Bone ($n = 33$)	Lung ($n = 27$)	Bone and ($n = 11$)	Viscera ($n = 14$)	ANOVA[a] P value
CEA (ng/ml)	40.5 ±134.8	14.5 ± 28.0	22.4 ± 36.2	32.9 ± 82.4	0.7215
ESR (mm/h)	36.2 ± 31.2	29.8 ± 24.4	28.7 ± 23.6	37.4 ± 30.5	0.7188
FERR (ng/ml)	305.9 ±525.8	242.0 ±506.3	261.2 ±275.4	970.0 ±1243.5	0.0078
CRP (mg/l)	31.3 ± 41.9	17.5 ± 26.0	35.5 ± 68.6	36.1 ± 43.9	0.4484
ORO (g/l)	1.55 ± 0.67	1.41 ± 0.45	1.44 ± 0.62	1.71 ± 0.94	0.5517

[a] Analysis of variance

Table 3. UICC response at 6 months versus marker score at 2 months (marker change > ± 10% pretreatment value)

Marker and UICC assessment	Marker index score		Fisher's exact (P value)
	≤0	>0	
CEA measured (n) = 63			
CEA >6 ng/ml (n) = 29			
Response/static	10	3	0.039
Progression	6	10	
ESR measured (n) = 63			
ESR >20 mm/h (n) = 39			
Response/static	17	1	0.037
Progression	14	7	
CRP measured (n) = 63			
CRP >10 ng/ml (n) = 33			
Response/static	13	3	0.38
Progression	12	5	
ORO measured (n) = 63			
ORO >1.2 g/l (n) = 35			
Response/static	14	3	0.64
Progression	15	3	
FERR measured (n) = 63			
FERR >200 ng/ml (n) = 25			
Response/static	7	3	0.47
Progression	9	6	

There was no significant difference between the pretreatment serum concentration for each marker and the dominant site of metastases except for serum FERR (Table 2), which was significantly elevated in patients with visceral metastases. Patients with lung metastases had the lowest mean concentration for all five markers although this did not reach significance.

Changes in individual serum markers in patients with systemic disease

Of 65 UICC-assessable patients who survived beyond 3 months, 3 (5%) showed a complete response to systemic endocrine therapy, 19 (29%) showed a partial response and

Table 4. UICC response at 6 months versus marker score at 4 months (marker change > ± 10% pretreatment value)

Marker and UICC assessment	Marker index score		Fisher's exact (p value)
	≤0	>0	
CEA measured (n) = 57			
CEA >6 ng/ml (n) = 28			
Response/static	9	2	0.004
Progression	4	13	
ESR measured (n) = 57			
ESR >20 mm/h (n) = 33			
Response/static	15	0	0.036
Progression	13	5	
CRP measured (n) = 57			
CRP >10 ng/ml (n) = 28			
Response/static	12	0	0.044
Progression	11	5	
ORO measured (n) = 57			
ORO >1.2 g/l (n) = 32			
Response/static	14	1	0.35
Progression	14	3	
FERR measured (n) = 57			
FERR >200 ng/ml (n) = 22			
Response/static	4	4	0.55
Progression	8	6	

10 (15%) had static disease, in all three groups the duration of response or static disease was at least 6 months; 49% of patients therefore had non-progressive disease (response + static) of a minimum duration of 6 months. A total of 51% of patients showed progression of disease within 6 months of therapy. In this study patients with responding and static disease at 6 months had similar survival, which was significantly longer than the survival of patients who have progressive disease within 6 months of commencing endocrine therapy. Patients with responding or static disease have been grouped together as one "non-progressive disease" group and compared with patients with progressive disease within 6 months of commencing systemic therapy.

Sequential change in a marker greater than the CV of the marker assay was regarded as significant, as in our retrospective study [43], i.e., a change of greater than ± 10% of the baseline pretreatment value. The cut-off values used to determine whether patiens were biochemically assessable were also the same as used in the retrospective study; i.e. CEA 6 ng/ml, ESR 20 mm/h, CRP 10 mg/l, ORO 1.2 g/l and FERR 200 ng/ml. Results comparing the UICC-assessed response at 6 months and changes in each of these five markers individually at 2, 4 and 6 months are shown in Tables 3–5.

The data were re-analysed taking a change in the marker concentration of 10% over and above the CV (i.e. a change of more than ±20% for each marker) as significant. Changes in CEA and ESR again correlated significantly at 2, 4 and 6 months (Table 6). There was no correlation between response and changes in ORO or FERR at any of these times while response correlated with changes in CRP only at 4 months (unpublished data).

Table 5. UICC response at 6 months versus marker score at 6 months (marker change > ± 10% pretreatment value)

Marker and UICC assessment	Marker index score		Fisher's exact (*P* value)
	≤0	>0	
CEA measured (*n*) = 58			
CEA >6 ng/ml (*n*) = 28			
Response/static	11	2	<0.001
Progression	3	12	
ESR measured (*n*) = 58			
ESR >20 mm/h (*n*) = 37			
Response/static	16	3	0.03
Progression	9	9	
CRP measured (*n*) = 58			
CRP >10 ng/ml (*n*) = 35			
Response/static	14	3	0.16
Progression	11	7	
ORO measured (*n*) = 58			
ORO >1.2 g/l (*n*) = 36			
Response/static	15	2	0.15
Progression	13	6	
FERR measured (*n*) = 58			
FERR >200 ng/ml (*n*) = 24			
Response/static	6	4	0.22
Progression	5	9	

Table 6. UICC response at 6 months versus marker score (Marker change > ± 20%)

Pre-treatment value and UICC assessment	Marker index score		Fisher's Exact (*P* value)
	≤0	>0	
Versus 2 months			
CEA measured (*n*) = 63			
CEA >6 ng/ml (*n*) = 29			
Response/static	10	3	0.039
Progression	6	10	
ESR measured (*n*) = 63			
ESR >20 mm/h (*n*) = 39			
Response/static	15	3	0.21
Progression	14	7	
Versus 4 months			
CEA measured (*n*) = 57			
CEA >6 ng/ml (*n*) = 28			
Response/static	9	2	0.004
Progression	4	13	
ESR measured (*n*) = 57			
ESR >20 mm/h (*n*) = 33			
Response/static	15	0	0.036
Progression	13	5	
Versus 6 months			
CEA measured (*n*) = 58			
CEA >6 ng/ml (*n*) = 28			
Response/static	10	3	0.004
Progression	3	12	
ESR measured (*n*) = 58			
ESR >20 mm/h (*n*) = 37			
Response/static	16	3	0.014
Progression	8	10	

Discussion

Carcinoembryonic antigen

CEA is the most investigated single marker in breast cancer. It has been shown that CEA measurements have no place in screening or in the diagnosis of early primary breast cancer [4, 10, 12, 22, 28, 32, 39]. Most vertical studies (i.e. studies examining serum CEA levels in different groups of patients with different stages of disease) have shown that the percentage of patients with elevated serum CEA levels increases with stage of disease, and that elevation of CEA is particularly noticeable in systemic disease [7, 9, 12, 16, 33, 37, 38]. This study prospectively confirmed that significant elevation of CEA was confined to the group of patients with symptomatic metastatic breast cancer.

This elevation of serum CEA raises its potential value in the diagnosis of metastatic disease. Some studies have reported that elevation of serum CEA in patients with secondary breast cancer is associated with the site of metastases [5, 14, 23, 26, 34, 35, 41]. However, there is no agreement between these studies as to which sites of disease are associated with elevated serum CEA levels. This present study has also been unable to show any correlation between serum CEA concentration and site of initial metastases (Table 2).

A number of studies have now reported a positive correlation between changes in serum CEA and response to systemic therapy in patients with metastatic breast cancer [3, 11–13, 17, 19, 20, 23, 24, 27, 34, 36, 41]. Assessment of changes in serum CEA is different between all these studies and in no study is there prospective confirmation of any one method of assessment. In this prospective study changes in serum CEA at 2, 4 and 6 months correlated significantly with the UICC-assessed response to endocrine therapy at 6 months (Tables 3–6) confirming this method of assessing response using serum CEA levels. At 4 months 28 of 57 (49%) patients were biochemically assessable: in 22 of these 28 (85%) patients, serum CEA changes correlated with the UICC-assessed response.

Ferritin

Marcus and Zinberg reported that elevation of FERR was found in serum of patients with breast cancer and that this appeared to be related to stage of disease [25]. Coombes et al. in a vertical study reported that 88% of patients with metastatic disease had elevated levels [6, 7] and Bezwoda and colleagues reported that FERR was elevated in the serum of patients with metastatic breast cancer [1]. From our unit Williams and colleagues reported that serum FERR was significantly elevated in patients with systemic breast cancer and that changes in serum FERR showed a highly significant correlation with the UICC-assessed response [43].

This study showed that serum FERR is significantly elevated only in patients with metastatic breast cancer (Fig. 5). There was a significant difference between the mean serum FERR and the site of initial metastases

(Table 2), the lowest mean concentration being for lung metastases and the highest for hepatic metastases. The retrospective study by Williams and colleagues reported that there was a significantly lower FERR concentration in patients with lung metastases than in all other groups [42], while Bezwoda reported that high concentrations of serum FERR (>400 μg/l) were always associated with liver metastases [1].

This study was unable to confirm prospectively the strong correlation found in the previous retrospective study between therapeutic response and change in serum FERR in patients with systemic disease [43].

Orosomucoid

Our retrospective study reported that serum ORO was elevated in patients with systemic breast cancer and that changes in serum ORO correlated significantly with response to therapy [43]. Roberts and colleagues reported that 18 out of 24 (62%) patients with metastatic disease had an elevated serum ORO value (>0.88 g/l) at diagnosis of systemic disease [29]. However, the lack of specificity of orosomucoid even in advanced breast cancer was shown by the fact that the mean serum ORO concentration of patients with Crohns disease was higher than the mean value of patients with disseminated breast cancer.

This study confirms previous reports that serum ORO is elevated in patients with systemic breast cancer. However, noting the lack of specificity shown by Roberts and colleagues [29] it is perhaps not surprising that our prospective study did not confirm a significant correlation between changes in serum ORO and therapeutic response.

C-reactive protein

Coombes and colleagues reported CRP to be a useful marker in the early detection of metastases in patients with breast cancer [6]. The upper limit of normal in that study was reported as 10 mg/l. Of patients with overt metastatic breast cancer, 81% showed elevation of CRP in serum. Another study reported that the percentage of patients showing an elevated serum CRP value (>10 mg/l) increased with stage of disease, 13% being elevated in stages I–III compared to 42% in stage IV. More recently CRP has again been reported to be elevated (>8 mg/l) in patients with metastatic breast cancer compared to breast cancer patients with primary or locally recurrent disease only [42]. Our retrospective study reported that serum CRP was elevated in patients with systemic breast cancer and also that changes in serum CRP correlated significantly with the UICC-assessed response [43].

This study confirms the retrospective analysis of Williams that serum CRP is elevated in patients with systemic breast cancer. There was no correlation between serum CRP and the site of initial metastases. The UICC-assessed response correlated with changes in serum CRP only at 4 months. Since changes in CRP at both 2 and 6 months showed no correlation with therapeutic response, CRP would not appear to be of clinical value in measuring response to therapy in advanced breast cancer.

Erythrocyte sedimentation rate

ESR was studied in patients with breast cancer by Coombes et al., who found elevated levels (>50 mm/h) in 16% of patients with metastases [8]. In combination with nine other markers ESR did not contribute significantly to the detection of metastases. A subsequent study reported a significantly elevated ESR in patients with breast cancer [21]. Our early data showed that ESR was significantly elevated in patients with systemic breast cancer and that changes in ESR correlated significantly with response to therapy [43].

This study confirmed that ESR is elevated in patients with systemic breast cancer. There was no correlation between ESR and the site of metastases. However, changes in ESR at 2, 4 and 6 months correlated significantly with therapeutic response. At 4 months 33 of 57 (58%) patients were biochemically assessable: in 20 of these 33 (61%) patients serum ESR changes correlated with the UICC-assessed response.

Conclusion

Few workers have reported retrospective analysis of serum markers in breast cancer with subsequent prospective confirmation. In this prospective study all five markers were significantly elevated in patients with symptomatic metastatic breast cancer and only changes in serum CEA and ESR correlated significantly with the UICC-assessed response to therapy. Confirmation both of this method of measuring changes in serum CEA and ESR and of their correlation with the UICC-assessed response to therapy provides the basis for using these markers in the assessment of response to therapy of distant metastases.

Acknowledgements. We are grateful to Dr. C. B. Marenah for use of the laboratory facilities in the department of Clinical Chemistry, City Hospital, Nottingham and to Miss Julie Meakin for performing the ferritin measurements. CEA measurements were performed by Dr. M. Price and funded by Cancer Research Campaign. Orosomucoid was measured by Mr. R. Namkaris, Department of Clinical Chemistry and C-reactive protein by Miss Nora Richards, Department of Immunology, University Hospital, Nottingham.

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