Pergamon

European Journal of Cancer, Vol. 35, No. 1, pp. 47–53, 1999

Printed in Great Britain
0959-8049/99/$ - see front matter

PII: S0959-8049(98)00297-4

Original Paper

The Objective Measurement of Remission and Progression in Metastatic Breast Cancer by use of Serum Tumour Markers

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An established biochemical index for monitoring therapy in patients with metastatic breast cancer was tested prospectively in a multicentre study. The index uses two serum tumour markers—carcinoembryonic antigen (CEA) and carbohydrate antigen 15-3 (CA15-3) along with erythrocyte sedimentation rate (ESR). 67 patients treated by either endocrine or chemotherapy had CA15-3, CEA and ESR measured at diagnosis of metastases and sequentially during therapy. Two markers, CA15-3 and CEA, were measured on a further 16 patients giving a total of 83 patients who were assessable for CA15-3 and CEA. Of the patients with CA15-3, CEA and ESR measured at diagnosis of metastases 84% (56/67) had elevation of 1 or more markers. During therapy the number with elevated marker(s) rose to 96% (64/67). Changes in the markers were in line with and often pre-dated therapeutic outcome as assessed by the International Union Against Cancer (UICC) criteria both for remission and progression. Patients without elevation of markers on diagnosis subsequently showed a rise in the marker(s) at or before documented disease progression by UICC. The 3 women in whom markers were at no time significantly elevated remain in remission. The results using CA15-3 and CEA were similar but 12% less patients were assessable. CA15-3 and CEA (with and without ESR) provide an objective method to guide therapy in patients with metastatic breast cancer. © **1999 Elsevier Science Ltd. All rights reserved.**

Key words: breast cancer, metastatic, tumour markers, monitoring therapy
Eur J Cancer, Vol. 35, No. 1, pp. 47–53, 1999

INTRODUCTION

BLOOD MARKERS are an established method of monitoring systemic therapies in a number of cancers, e.g. βHCG in choriocarcinoma, βHCG and αFP in testicular cancer and CA125 in ovarian cancer. The potential use of blood markers to monitor systemic therapy in breast cancer is at present confined to patients with metastatic disease. A number of groups have reported studies in this latter area but virtually all have been retrospective analyses: even in studies where the clinical data and samples were collected prospectively the method of calculating significant changes in the markers was derived retrospectively by comparing marker changes to the current standard method for guiding therapy, i.e. the UICC (International Union Against Cancer) criteria. Retrospective analysis of data gives rise to 'best fit' results. It is not surprising in such studies that changes in tumour markers (whatever markers may be reported) often appear impressive and show good correlation with UICC criteria [1–5].

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Received 9 Feb. 1998; revised 20 Jul. 1998; accepted 28 Jul. 1998.

To the authors' knowledge only two methods for assessing changes in blood markers have been retrospectively derived and then prospectively validated on new groups of patients with metastatic breast cancer. Using one method changes of 50% decrease or 25% increase in a tumour marker concentration compared to the pretreatment value were regarded as significant for three markers, CA15-3, CEA and TPS [6, 7]. However, in both studies the authors compared the results of each individual marker rather than offering a method of combining the three markers. The other prospectively validated method of interpreting changes in three markers (CA15-3, CEA and ESR) combined the results of the three markers into a single biochemical index. The results obtained using this method have been reported for monitoring both first- and second-line endocrine and chemotherapy [8–11]. The method has also been used as the sole means of directing hormone and/or chemotherapy in two small randomised studies [11, 12].

This work has until now been carried out at a single centre. The present study extends the confirmation of the method to a multicentre setting in six European countries. The study was carried out between July 1994 and August 1995.

PATIENTS AND METHODS

The study involved 11 centres from 6 European countries. Patients were eligible for the study if they had newly diagnosed distant metastatic breast cancer with at least one lesion assessable according to UICC criteria [13]. Patients were treated at each centre with either hormone therapy or chemotherapy according to local treatment protocols. Assessment of therapeutic response by UICC criteria was performed at 3 monthly intervals or earlier if clinically indicated. Blood was withdrawn at each assessment visit for measurement of the three tumour markers—CA15-3, CEA (carcinoembryonic antigen) and ESR (erythrocyte sedimentation rate).

ESR was measured locally in 8 of the 11 participating centres. With the exception of one centre CA15-3 and CEA were measured centrally (Nottingham) using the Centocor CA15-3™ RIA assay and the CIS CEA assay. The CA15-3 and CEA measurements were performed by persons who had no knowledge of the clinical outcome.

The CVs between replicates of the same sample had to be below 10% for the results to be acceptable. The only exceptions were very low values at the lower limit of an assay (i.e. well below the cut-off level chosen for the assay) where small absolute differences between replicates of no clinical significance give high CV values (e.g. CEA replicate measurements of 1 and 2.0 μg/l where the cut-off level = 6 μg/l).

127 patients with newly diagnosed metastatic breast cancer were registered for the study. Of these, 4 had registration details only whilst 123 patients had blood marker measurements carried out on at least the pretreatment samples. This paper reports on the patients who had sequential tumour marker measurements to compare with clinical outcome.

83 patients had CA15-3 and CEA measured both before and during therapy, of whom 67 also had ESR measured. As noted above, 3 of the 11 centres did not measure ESR locally. The 83 patients received a spectrum of systemic therapies representative of current treatments for metastatic breast cancer: tamoxifen ($n = 14$), goserelin and tamoxifen ($n = 5$), megestrol acetate ($n = 6$), Onapristone (progesterone antagonist) ($n = 5$), aromatase inhibitors ($n = 4$), unspecified hormone agent (n = 4), CMF (cyclophosphamide, methotrexate and 5-fluorouracil) ($n = 10$), anthracycline-based regimens ($n = 8$), paclitaxel ($n = 5$), unspecified chemotherapy ($n = 1$), hormone agent + bisphosphonate or placebo ($n = 10$), chemotherapy + bisphosphonate or placebo ($n = 2$), GnRH analogue ($n = 1$). The systemic therapy was not specified in 8 patients.

UICC assessment

The efficacy of hormone therapy or chemotherapy was assessed using the UICC criteria [13]. Assessments were carried out at baseline (pretreatment) and then at 3 monthly intervals. Patients were classified as showing complete response (CR), partial response (PR), static disease (SD) or progressive disease (PD).

It has previously been reported that the survival of patients with durable SD is statistically no different to patients who have a PR [14–16]. As in our previous publications, we combined patients with CR, PR and SD into one group (non-progression) and compared them with patients with PD (progression) [8, 9].

Biochemical assessment

Scoring system. The method for calculating the combined biochemical score from changes in individual serum markers was the same as previously reported [8–12]. In summary, a cut-off level for each individual marker of the mean ± 2 S.D. of a normal control population of women had previously been established. These cut-off levels are shown in Table 1. Any initial change in a marker while the patient was on therapy was related to the pretreatment baseline value of the marker. Biochemical progression was where either a marker started below the cut-off level and moved above it or, if the marker concentration started above the cut-off level, it increased by more than 10% of the baseline value. Biochemical response was the opposite, i.e. a marker which started above the cut-off level at baseline and fell either by greater than 10% or fell below the cut-off level. Biochemically stable markers were where the marker started above the cut-off level and increased or decreased by $\leq 10\%$ of the baseline value. If marker measurements started and remained below the cut-off level then that marker was counted as non-contributory or a 'non-elevated marker' (NEM). Patients where the three markers at baseline were classified as NEM are reported as a separate group to establish whether one or more markers rise at or before progression by the UICC criteria.

As in our previous reports [8–12] where changes in CA15-3 or CEA indicated 'biochemical response', each were scored as − 2 whilst ESR was scored as − 1 (Table 1). Where changes in any of the three markers indicated 'biochemical progression' each marker was scored as + 2 (Table 1). Each marker which was regarded as 'biochemically stable' was given a score of + 1 (Table 1). Unlike clinically assessed SD which behaves like CR or PR, it has previously been noted and reported that a biochemically 'stable' marker was not indicative of disease which was in remission—thus, the score of + 1. Table 1 summarises the cut-off levels and the scoring for each of the three markers. The maximum and minimum scores for biochemical progression or response where all three markers were contributory were + 6 and − 5, respectively. As reported in previous publications a score of > 0 indicates progression while a score ≤ 0 indicates non-progression [8–12].

Table 1. *Scores for changes in marker concentrations*

	Upper limit of normal	Non-elevated marker (NM)	Decrease (> 10% decrease)*	Stable (≤ 10% increase or decrease)*	Increase (> 10% increase)*
CEA	$6\,\mu g\,l^{-1}$	0	−2	+1	+2
CA15-3	$33\,KU\,ml^{-1}$	0	−2	+1	+2
ESR	$20\,mm\,h^{-1}$	0	−1	+1	+2

NB: Overall biochemical score was summation of the individual score for each marker. *The data were also analysed using a 20% change in markers as significant (see text and tables for details).

Analyses using 10 *and* 20% *change.* In all our previous publications, we reported a 10% change in each marker as significant. It has been suggested that a minimum change of 20% should be used. In one previous publication, we presented data for both a 10 and 20% change [9] and showed similar results. We again present the data for a 10 and 20% change in marker concentrations for CA15-3, CEA and ESR in combination.

*CA*15-3/*CEA*/*ESR.* The biochemical index, as retrospectively derived and prospectively confirmed, uses the three markers in combination. The results for the three markers together will, therefore, be presented first focusing on the 67 patients in whom changes in the three markers versus UICC criteria could be compared.

*CA*15-3/*CEA combination.* The study data were also analysed and presented using only CA15-3 and CEA. As already noted, some centres did not measure ESR. Secondly, CA15-3 and CEA are tumour associated antigens whereas ESR is not. The data for the CA15-3/CEA combination are shown essentially in the same format as reported above for the three markers.

Presentation of results. For each analysis of the data, patients were divided into two groups: those who progressed during the study and those who remained in remission throughout the study. Patients 'belong to' one group and were not moved between the two groups.

1. Confirmed progression of disease, i.e. patients who progressed during the study (even if they had a period of remission initially).

   UICC progression reflected either *de-novo* resistance or occurred after a period of disease remission (i.e. acquired resistance). Either way where UICC progression occurred, a full comparison with the changes in tumour markers was possible. For example, do the markers detect early disease progression? Do they measure any initial period of response and in such circumstances do they give lead time in detecting progression due to acquired resistance? Since a more complete clinical comparison can be made, the data on patients who developed disease progression during the study are presented first.
2. Continued therapeutic remission, i.e. patients who remained in remission throughout the study period.

   Data on patients who remained in remission throughout the study period are shown separately. This excludes patients who showed an initial period of remission followed by disease progression before the end of the study. The latter are reported under group 1. where the clinical outcome was completed and therapy changed. So as not to show the same patient data twice, group (2) contains only patients who remained in remission up to and including the last recorded clinic visit. Correlation of marker changes in patients where the disease remains in remission can be difficult. For example, if a patient in remission shows a rising marker, particularly at the last follow-up visit, it leaves open the possibility that this is an early indication of subsequent disease progression. We have sought clinical follow-up data on such patients detailing their clinical course after the end of the study period, particularly to establish if they showed progression of disease.

RESULTS

*CEA, CA*15-3 *and ESR*

The number of patients with one or more of these three markers elevated *at diagnosis* of metastases is shown in Table 2. Of the 67 patients, 50 (75%) had elevation of CA15-3 and/or CEA. With the addition of ESR this figure rose to 56 (84%). These 67 patients had sequential measurements of the three markers *during therapy*. 57 (85%) had elevation of CA15-3 and/or CEA during therapy (Table 2). With the addition of ESR this figure rose to 64 (96%). Three patients (4%) showed no elevation of any marker before or during therapy—all remained in remission throughout the study period.

Correlation of three markers and UICC defined disease progression (PD) (n = 39). Comparison between the biochemical score and UICC assessed PD are shown in Table 3. These results were identical whether a 10 or 20% change in marker concentration was taken as significant. Overall, changes in the three tumour markers reflected UICC-defined disease progression in 34 out of 39 patients (87%), and these are detailed below.

UICC PD before 6 *months* (n = 22). In 19 (86%) patients the biochemical score (using either a 10 or 20% change as significant) indicated disease progression at the time the UICC criteria indicated progression. In the other 3 patients the biochemical marker score was falling at 3 months when the UICC criteria indicated disease progression.

UICC PD at 6 *months* (n = 13). A further 13 patients were diagnosed at the 6 month assessment as having disease progression by UICC criteria. 12 of these patients had marker measurements at 3 months and 11 of them at 6 months. Of the 11 patients with tumour markers measured at 6 months (Table 3), 10 (91%) showed changes which reflected disease progression by UICC. In one other patient there was a decrease in ESR which did not reflect clinical outcome. 12 patients had tumour markers measured at 3 months (data not shown). 9 patients (75%) showed changes which predicted the UICC progression at 6 months. In the other 3 (25%) patients the tumour marker changes at 3 months reflected the UICC status at that time (i.e. static disease or objective

Table 2. Number of patients (%) with elevated marker(s)

		NM	CA15-3	CEA	ESR	CEA ESR	CA15-3 CEA	CA15-3 ESR	CA15-3 CEA ESR
At diagnosis ($n = 67$)	*n*	11	36	28	27	40	50	50	56
	(%)	(16)	(54)	(42)	(40)	(60)	(75)	(75)	(84)
During therapy ($n = 67$)	*n*	3	47	40	46	49	57	61	64
	(%)	(4)	(70)	(60)	(69)	(73)	(85)	(91)	(96)

NM, non-elevated markers.

response). In 2 of these 3 patients the biochemical score was > 0 by 6 months when UICC progression was detected.

UICC PD after 6 months (n = 4). 2 patients developed PD by UICC criteria at 9 months (Table 3). In both patients the tumour markers fell at 3 months (score ≤ 0) but were rising again both at 6 and 9 months (score > 0). In 2 patients who developed PD at 12 months the tumour marker index score indicated biochemical response (i.e. ≤ 0) at 3 and 6 months followed by biochemical progression (score > 0) at 9 and 12 months (Table 3 shows score at 12 months).

Correlation of the three markers and UICC defined disease remission (DR) (n = 28). Comparison between the biochemical score and UICC assessed DR are shown in Table 4. These results were identical whether a 10 or 20% change in marker concentration was taken as significant. Overall, changes in the three tumour markers reflected UICC-defined remission in 19 out of 28 patients as detailed below.

UICC DR at 3 months (n = 5). 5 patients were in remission with only 3 months clinical follow-up. 3 patients had a score ≤ 0 and 1 patient had normal markers (score 0): in 4 patients, therefore, the biochemical score matched the UICC criteria. The fifth patient had a score of > 0. Follow-up of this last patient has shown that her disease progressed 9 months after starting treatment. Tumour markers continued to rise in this patient at 6 months and at 9 months. In this patient the markers gave a 6 month lead time for detection of progressive disease.

UICC DR at 6 months (n = 14). A positive correlation between tumour marker changes at 6 months and UICC criteria was seen in 7 out of 13 (54%) patients (Table 4). In the remaining 6 patients the score was increasing (Table 4): in fact in 4 of these 6 patients the score showed consecutive rises at 3 and 6 months. Further clinical follow-up has been obtained in all 6 patients: 1 patient died within 6 months, 4 showed PD 2, 3, 8 and 9 months after the study closed whilst the remaining patient showed no evidence of PD after 18 months follow-up.

Table 3. Biochemical scores (CA15-3, CEA and ESR) compared with UICC progressive disease (months)

	UICC PD (months)			
	2–4	6*	9	12
Biochemical score				
> 0	19	10	2	2
≤ 0	3	1	0	0

10 and 20% change in markers gave identical results. *2 other patients with UICC PD at 6 months did not have marker measurements at 6 months.

UICC DR at 9 months (n = 8). At 9 months all 8 patients had a score ≤ 0 or score NEM (0) in keeping with their UICC status (Table 4). At 6 months 7 patients showed a score ≤ 0 or score NEM (0), in keeping with the UICC status. The remaining patient showed a rise in one tumour marker which came back down at 9 months. There is no follow-up beyond 9 months on this patient.

UICC DR at 12 months (n = 1). One further patient remained in remission for up to 12 months. The biochemical scores for a 10% change were a score of ≤ 0 at 3 months and a score > 0 at 6 and 12 months. Using a 20% change the scores were ≤ 0 at 3 and 6 months and score > 0 at 12 months (Table 4 shows 12-month result).

Non-elevated baseline marker (NEM) measurements. Table 2 shows that 11 out of 67 patients (16%) had no elevation of any of the 3 markers on baseline measurement i.e. before starting treatment. During treatment 3 patients (4%) continued to show no elevation throughout the course of the study: all remain in disease remission at last clinical follow-up. The remaining 8 (12%) patients who had non-elevated marker measurements at baseline did show disease progression (by UICC criteria) during the course of the study: all 8 patients showed a score > 0 (indicating biochemical progression) either at or before progression was diagnosed by UICC.

CEA/CA15-3

83 patients had CA15-3 and CEA measured before and during therapy. 61 of these (73%) patients showed an elevation of 1 or both markers before starting treatment (i.e. baseline marker measurements). 70 (84%) patients showed an elevation of 1 or both before or during treatment such that it allowed comparison of tumour marker changes with UICC.

Correlation of only CEA/CA15-3 and UICC defined disease progression: UICC PD before 6 months. 29 patients showed disease progression within 6 months of starting treatment. 24 patients (83%) showed a score of > 0 in keeping with the

Table 4. Biochemical scores (CA15-3, CEA and ESR) compared with UICC disease remission (months)

	UICC DR (months)			
	3	6	9	12
Biochemical score				
> 0	1	6		1
≤ 0	3	6	6	
NEM (0)	1	1	2	

10 and 20% change in markers gave identical results. *Further clinical follow-up data on those 8 patients showed that 7 had PD between 2 and 9 months after the study closed and 1 remained in SD after 18 months follow-up.

Table 5. Biochemical scores (CA15-3 and CEA) at 3 and 6 months compared to UICC PD at 6 months

	Time of tumour marker measurements	
	3 months	6 months
Biochemical score		
>0	8*	10*
≤ 0	1†	0
NEM (0)	5†	3

*Predicted at 3 months UICC disease progression at 6 months. †Reflected UICC non-progression at 3 months.

UICC criteria. The other 5 showed a score ≤ 0. Details of 3 of these patients were described above in the similar section reporting the 3 marker combination. In the fourth patient CA15-3 and CEA moved in opposite directions (increasing and decreasing, respectively) cancelling each other out and resulting in a score = 0. In this patient ESR had increased and proved useful in confirming disease progression. The fifth patient showed a fall in CA15-3 at 3 months which rose by 6 months.

UICC PD at 6 months. 15 patients had progressive disease diagnosed at 6 months: 12 had markers measured both at 3 and at 6 months; two had markers measured only at 3 months; and one only at 6 months. There are, therefore, marker scores at 3 months on 14 out of the 15 patients and at 6 months on 13 out of the 15 patients (Table 5). 10 patients showed marker score >0 at 6 months in keeping with the PD UICC criteria at 6 months (Table 5): 8 of these 10 patients showed marker rises even at 3 months predicting disease progression. 3 patients showed non-elevation of CA15-3 or CEA even by the time of disease progression at 6 months (Table 5).

UICC PD after 6 months. 6 further patients showed disease progression by UICC after 6 months treatment—2 patients after 9 months and four at 12 months. In only 3 of these patients did the two markers alone detect progression before the UICC criteria.

Correlation of only CEA/CA15-3 and UICC defined disease remission: UICC DR at 3 months. 5 patients were in remission after only 3 months follow up. The results with only CEA/CA15-3 were similar to when 3 markers were used (see above).

UICC DR at 6 months. A further 17 patients were assessed as in disease remission at 6 months by UICC criteria: 14 patients had markers measured both at 3 and at 6 months; 2 other patients had tumour markers measured at 3 months only; and 1 other at 6 months only. There were, therefore, a total of 16 patients with marker measurements at 3 months and 15 patients at 6 months. Results are shown in Table 6. 10 out of 15 patients (66%) again showed a score ≤ 0 at 6 months, in keeping with the UICC status. The remaining 5 patients showed a score >0. 2 of these 5 patients had also shown a rise at 3 months which continued to increase at 6 months.

Table 6. Biochemical scores (CA15-3 and CEA) at 3 and 6 months compared with UICC DR at 6 months

	Time of tumour marker measurement	
	3 months	6 months
Biochemical score		
>0	5	5
≤ 0	8	8
NEM (0)	3	2

Table 7. Biochemical scores (CA15-3 and CEA) at 6 and 9 months compared with UICC DR at 9 months

	Time of tumour marker measurements	
	6 months	9 months
Biochemical score		
>0	1	1
≤ 0	5	4
NEM (0)	4	4

UICC DR at 9 months. 11 more patients were assessed to be still in disease remission by UICC criteria at 9 months follow-up. 8 of these patients had markers measured both at 6 months and at 9 months, 2 patients had markers measured only at 6 months and 1 patient only at 9 months. There are, therefore, marker scores at 6 months on a total of 10 patients and at 9 months on 9 patients. 9 out of 10 (6 months) and 8 out of 9 (9 months) patients showed score ≤ 0 or score NM (0) at 6 and 9 months, respectively, in keeping with UICC status (Table 7). In the remaining patients the rising tumour markers were early signs of what subsequently was shown to be disease progression.

DISCUSSION

There was an excellent correlation between changes in the 3 tumour markers and disease progression by UICC criteria (Table 3). Our results show that, for progression defined by UICC criteria, changes in tumour markers reflected the UICC status in 33 out of 37 patients. In 3 patients the markers were falling at 3 months (when UICC showed PD) and may, therefore, have resulted in a short delay in diagnosis of disease progression. For example, in 1 of these 3 patients who was continued on the same therapy the index score had risen by 6 months.

In 17 patients progressive disease (by UICC criteria) was identified at later time-points (i.e. from 6–12 months after starting treatment). In 24% of these patients the marker changes mirrored the UICC assessment, i.e. the marker score rose at the same time as progression was detected by the UICC criteria. However, in 13 patients (76%) the tumour marker rises were recorded between 3 and 9 months before disease progression was detected by UICC criteria. The study, therefore, showed that tumour markers can be used for the detection of disease progression and in a significant majority of patients will detect progression before the UICC criteria.

We also showed that tumour marker changes will predict remission. This information can be useful to reassure patients early that a treatment is being effective and can also encourage the clinician to persevere with a particular therapy. In future such early detection of remission may be particularly important in devising treatment strategies involving new and expensive chemotherapeutic agents (e.g. taxanes). If remission can be predicted after, for example, 2 cycles the patient would be continued on the treatment. However, if the markers were rising the therapy could be discontinued, at one

and the same time, saving costs on drug therapy and benefiting the patient, who would not have to suffer prolongation of drug side-effects from an ineffective treatment.

In patients who show remission of disease by UICC criteria one caveat should be mentioned. In 2 patients there was a transient rise at 3 months in a single assessable marker (CA15-3 in one and CEA in the other patient). There was no evidence of progressive disease by UICC criteria with these rises. Both patients were in disease remission by UICC criteria at 6 months and in both patients the marker had decreased at 6 months. Transient rises ('spiking') have been reported [17] to occur during the first few weeks in some patients who subsequently show a good response to treatment [17]. It has been postulated that such 'spiking' is the result of tumour lysis. The markers appear to rise precipitously within the first month and start to decline thereafter. By 2 or 3 months after starting therapy it may not have fallen significantly below the pretreatment value. Whilst such 'spiking' appears to involve a small number of patients, an early change of treatment would deny such patients the benefit of an effective therapy. Measurement of an additional blood sample between 3 and 6 weeks after starting treatment would help interpret any rise in the markers at 3 months as either 'spiking' or due to persistent increases in the marker(s).

Correlation of marker changes with disease remission is more difficult than with disease progression. The latter is a clinical endpoint for changing therapy and one can judge changes in tumour markers up to that time-point. However, if a patient is in remission at the last follow-up, a rising tumour marker, particularly at the last visit, leaves open the possibility that this is an early indication of disease progression. This explanation is supported by the findings in this study. In a large percentage of patients where disease progression by the UICC criteria was detected, increases in the blood markers did precede the UICC criteria. Secondly, of the 8 patients where the biochemical score was increasing while UICC indicated SD or PR at the last routine clinic visit (Table 4), we have now obtained further clinical follow-up data: 7 of these patients showed PD between 2 and 9 months after the study closed (see results) and one remains in SD after 18 months follow-up.

This study has shown that all patients with UICC assessable metastatic breast cancer lesions can have their systemic therapy directed by changes in 3 blood markers used in combination, i.e. CA15-3, CEA and ESR. The method for monitoring changes in the markers has previously been retrospectively derived and prospectively confirmed in a single centre for both hormone and chemotherapy [8–12]. The present study has shown the accuracy of this method in a prospective evaluation of both the method and the 3 markers in combination in a European, multicentre context. The other prospectively tested method looked at 3 markers (CA15-3, CEA and TPS) [7]. Whilst the paper reported differing sensitivities and specificities for each marker individually, it did not present data for combining 2 or all 3 markers. It is, therefore, not possible to compare that study with the results of the present study. For example, we do not know whether combining CA15-3 and CEA could have given similar results with their methodology (i.e. 50% decrease/25% increase) as we report here with our methodology. It is also, therefore, not possible to assess and compare, in these studies, whether TPS would add more or less than ESR does to the combination of CA15-3 and CEA. However, the Nottingham group did compare adding TPS to CA15-3, CEA and ESR and found no benefit [18]. Equally, in that study ESR was reported to provide a better combination with CA15-3 and CEA than TPS did with CA15-3 and CEA [18].

A number of studies have reported that changes in TPS as a single marker correlate with therapeutic response [19–22]. Three out of four studies reported that changes in TPS occur earlier after starting treatment than changes in CA15-3 or CEA [19–21]. The fourth study reported that CA15-3 gave a longer lead time than TPS for the initial diagnosis of metastatic disease [22]. However, again all these studies compared TPS with CA15-3 [21, 22] or TPS with CA15-3 and CEA [19, 20] rather than presenting the results of using 2 or 3 markers in combination for monitoring therapy. Furthermore, none compares TPS with ESR as individual markers.

An important finding of the present study is that when the 3 markers (CA15-3, CEA and ESR) were used in combination, all patients presenting with distant metastatic disease were suitable for marker directed therapy. This includes the 16% of patients who had normal baseline measurements of all 3 markers. Twelve per cent of these developed disease progression by UICC criteria during treatment and in all these patients there was a biochemical score > 0 at or before disease progression was detected by UICC. The remaining 3 patients (4%) remained in remission throughout the study and all the markers remained below the cut-off levels. It appears, therefore, that all patients, even those without elevated marker measurements on baseline tests, can be entered into a marker directed therapy programme.

As noted above, we also analysed our data using only CA15-3 and CEA measurements. The results were very similar to the combination of 3 markers. However, using CA15-3 and CEA only, 73% of patients showed elevation of one or both markers on baseline measurement and only 84% of patients showed an elevation of one or both before or during therapy. The addition of ESR to CA15-3 and CEA allowed a further 12% of patients to be assessed during therapy (i.e. increase from 84% to 96%). In a prospective setting a clinician could only truly use CA15-3 and CEA in the 73% of patients where one or both were elevated before treatment began (i.e. at baseline measurement) since the clinician would not know the further 11% of patients who would show an elevation of CA15-3 and/or CEA during treatment (i.e. total 84% patients). When ESR was included in combination with CA15-3 and CEA all patients could have their therapy directed by changes in these three tumour markers. Therefore, the addition of ESR in effect increases the percentage of patients assessable by tumour markers in a clinical situation from 75 to 100%.

This study has confirmed the clinical utility of blood markers for directing systemic therapy in patients with metastatic breast cancer. Using two markers (CA15-3 and CEA) would only allow 75% of patients prospectively to have their therapy marker directed. CA15-3, CEA and ESR combination allowed all patients in this study to have their therapy marker directed. We have previously estimated the potential cost–benefit from monitoring therapy for metastatic breast cancer by blood markers compared to UICC criteria [23]. We believe that tumour marker directed therapy should be tested against UICC directed therapy in a multicentre randomised trial.

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Acknowledgement—This study was supported by a grant from Centocor Diagnostics.