Breast Cancer Research and Treatment (2006) 98: 241–248
DOI 10.1007/s10549-005-9155-y

Clinical trial

Prognostic significance of changes in CA 15-3 serum levels during chemotherapy in metastatic breast cancer patients

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Key words: advanced breast cancer, CA 15-3, clinical response, survival, tumor marker

Summary

Tumor response to first-line chemotherapy in advanced breast cancer offers prognostic information and may be used as a surrogate marker for evaluating treatment efficacy. With this study we wanted to determine whether changes in circulating serum CA 15-3 levels during chemotherapy provided additional information for prognostic prediction. Serum CA 15-3 was measured at baseline and after 3 and 6 months during anthracycline-based first-line chemotherapy in 526 patients with advanced breast cancer prospectively enrolled in five phase II-III trials. Changes in marker levels were correlated with disease response, time to progression and overall survival. In all, 336 patients attained a disease response. A significant relationship was found between disease response and CA 15-3 variations, although many individual discrepancies were also observed. At the 6-month time point, the median time to progression was 15.3 months in patients with normal marker levels throughout the study, 11.7 months in those with a CA15-3 reduction >25%, 9.6 months in those with elevated baseline CA 15-3 levels which did not change during therapy and 8.6 months in those with increased marker levels ($p < 0.001$). The median survival was 42.3, 29.7, 28.5, and 24.8 months, respectively ($p < 0.002$). The prognostic role of changes in CA 15-3 levels was maintained in the patient subset attaining disease response or stabilization to treatment ($p < 0.001$) and after adjusting for clinical response and major prognostic parameters in the multivariate analysis ($p < 0.001$). In conclusion, monitoring serum CA 15-3 levels during first-line chemotherapy in advanced breast cancer patients provides prognostic information independently from tumor response.

Introduction

Breast cancer remains the leading cause of death from cancer among women in Italy [1]. The natural history of advanced breast cancer has been widely studied, and prognostic factors such as disease free interval, estrogen receptor status of primary malignancy, liver metastases, previous adjuvant chemotherapy, and performance status have been defined [2–4]. These parameters are static.

During systemic antineoplastic treatment, metastatic breast cancer is usually monitored by imaging techniques, and disease response is assessed according to standardized criteria [5,6] based on changes in the size of measurable lesions.

In prospective clinical trials, patients responding to chemotherapy usually fare better and survive significantly longer than non responders [7,8]. Response to treatment can therefore be considered a dynamic prognostic parameter. Whether tumor response may also be a surrogate parameter of treatment efficacy has been questioned, since many patients experiencing an objective response may have a better outcome even without treatment [9]. Yet preliminary data seem to support this observation [10].

The product of the MUC-1 gene, known as CA 15-3, is a circulating tumor marker widely employed in monitoring breast cancer patients during systemic treatment [11–13] but its usefulness remains uncertain.

Table 1. Study designs of prospective trials and patient outcomes

Study No.	Author, year (Ref)	Study designs	Regimen		Patients (No.)	ORR (%)	TTP (months)*	Survival (months)*
1	Bumma et al., 1989 (23)	Phase III	FEC vs EPI	Total	130	55.6	9.8	29.6
				CA 15-3 evaluable	68	63.4	10.2	31.2
2	Alabiso et al., 1998 (22)	Phase II	TAX + EPI	Total	55	66.7	8.7	39.1
				CA 15-3 evaluable	42	61.5	9.1	40.9
3	Dogliotti et al., 1996 (24)	Phase III	EPI vs EPI + LND	Total	207	46.4	10.6	25.1
				CA 15-3 evaluable	152	56.5	10.1	25.3
4	Dogliotti et al., 1998 (25)	Phase II	EPI + LND + CDDP	Total	28	64.2	13.5	32.3
				CA 15-3 evaluable	22	66.9	12.0	31.8
5	Berruti et al., 2002 (26)	Phase III	EPI vs EPI + LND vs	Total	371	57.7	10.3	28.8
			EPI + CDDP vs	CA 15-3 evaluable	242	64.2	11.3	31.1
			EPI + LND + CDDP					
TOTAL				Total	791	58.2	10.2	28.4
				CA 15-3 evaluable	526	63.8	11.0	29.9

ORR denotes overall response rate; TTP time to progression; FEC fluorouracil, epirubicin, cyclophosphamide; TAX Paclitaxel; EPI epirubicin; LND lonidamine; CDDP cisplatin
*Kaplan-Meier product-limit median time estimations.

Several small studies have reported a good correlation between changes in serum CA 15-3 levels and response to therapy [14–19]. However, this raises the question of whether a tumor marker test that parallels response to therapy can aid in the clinical management of breast cancer patients [11]. With the exception of no readily measurable disease, the routine use of serum CA 15-3 levels in the management of metastatic breast cancer patients is not recommended by the American Society of Clinical Oncology guidelines [20] for several reasons, one being that serum CA 15-3 has a limited sensitivity (60–70%) [21]. A sizeable proportion of discordant results have been reported between changes in CA 15-3 levels and clinically assessed disease response [14]. In patients destined to attain a disease response, marker levels may transiently increase shortly after the start of treatment, leading to a false interpretation of the clinical course and the risk of removing the patient from effective chemotherapy [11].

With this study we wanted to demonstrate in a large population of metastatic breast cancer patients submitted to first-line chemotherapy that serial evaluation of serum CA 15-3 levels can provide additional prognostic information independently from that offered by disease response as assessed by the UICC (Union International Contre le Cancer) criteria. Should this be so, then variations in CA 15-3 concentrations may represent a new and useful tool for clinicians to predict the clinical course of their patients.

Patients and methods

Patients

From October 1988 to November 1999, 791 metastatic breast cancer patients were enrolled in five consecutive phase II-III multicenter trials of first-line chemotherapy with anthracycline-based regimens [22–26] (Table 1). The primary aim of the studies was to determine disease response or time to progression. After 3 and 6 months, treatment response was evaluated by clinical examination, abdominal computed tomography or ultrasonography, chest radiography, and skeletal x-ray when necessary. A complete biological profile was performed each month before administration of chemotherapy. Determination of serum CA 15-3 levels was strongly recommended but not compulsory. But because some study centers did not follow this recommendation, data on changes in CA 15-3 levels were not available for all the 791 enrolled patients (Table 1). Throughout the study, changes in marker level never influenced the treatment decision-making process. CA 15-3 levels were measured in different laboratories. So to minimize inter-laboratory variation, the marker level of each patient was assessed by the same laboratory.

Marker assay

Measurements of circulating serum CA 15-3 were carried out at baseline and after 3 and 6 months of therapy. CA 15-3 levels were evaluated using commercially available kits at 10 different laboratories certified by national data quality control programs. Two laboratories employed the automated MEIA Abbott IMx (Abbot Park, IL, USA), four the automated Boehringer–Mannheim Enzymun-Test (Tutzing, Germany), two the non-automated CIS ELISA (Tronzano – Vercelli, Italy) and two the non-automated IRMA Centocor (Malvern PA, USA). Interassay variability ranged between 9% and 12%. The average cost per single CA 15-3 determination was about US$25. The calculated upper normal concentration range was 30–35 U/l for the four methods. To simplify the analyses, 30 U/ml was considered the cut-off level. Changes in CA 15-3 concentrations after 3 and after 6 months of therapy are

expressed as a percentage of the baseline value computed according to the formula:

$$\frac{\text{CA 15-3 value} - \text{Initial CA 15-3 value}}{\text{Initial CA 15-3 value}} \times 100$$

Clinical variable evaluation

Treatment response was classified according to the UICC criteria (5). A complete response was defined as the complete disappearance of all clinically detectable malignant disease. A partial response was characterized as a ≥50% decrease in the sum of the products of the two longest perpendicular diameters of all measurable lesions and ≥50% recalcification of osteolytic lesions. Progressive disease was defined as an increase of at least 25% in the size of measurable lesions and the development of new lesions.

Time to progression was estimated from treatment start till progression or date of the last follow-up visit (30 June 2001). Survival time was calculated from treatment start to death or last follow-up. Patients alive or lost to follow-up at the time of data computation were censored at the time of the last follow-up examination.

Statistics

The areas under the receiver operating characteristic curve (ROC) were calculated as a measure of predictive discrimination of tumor response and progression by CA 15-3 variation. An index of 0.5 indicates no discrimination ability, whereas a value of 1 indicates perfect discrimination. The cut-off points of marker increase and decrease were identified according to the corresponding plotted curves.

The difference between proportions was evaluated by the chi-square test with Yates' correction, when necessary. Survival curves were plotted using the Kaplan-Meier method and statistically evaluated using the log-rank test. To reduce the inherent bias of assessing survival as a function of response, survival analysis was also performed with the landmark method [9]. Accordingly, patients were evaluated according to their response status at a fixed time after the initiation of therapy, regardless of any subsequent shift in tumor response status. Patients who went off protocol before the time of landmark evaluation were excluded from the analysis. Since the number of patients after 3 months into the study was the same as at baseline, a landmark point at month 6 was used. Multivariate survival analysis according to the Cox model was performed to eliminate confounding variables. Martingale and Schoenfeld residuals were used to check the adequacy of the linearity and the proportional hazard assumptions [27]. Variation in CA 15-3 levels was considered as a time-dependent covariate and was included as such in the model. Independent variables were categorized as follows: disease response to therapy = 3, stabilization = 2, progression = 1; CA 15-3 variation: CANE = 0, CAR = 1, CANC = 2, and CAP = 3. Estrogen receptor status positive = 1, negative = 0; Menopausal status: post = 1, pre = 0; Presence of liver, lung, bone, or soft tissue metastasis = 1, absence = 0. Statistical computations were performed using the SPSS for Windows [28] and STATISTICA for Windows software packages.

Results

Table 1 describes the outcomes of patients and specific trial designs of the five prospective studies. As shown, the 526 patients for which CA 15-3 determinations were available did not differ from the enrolled subjects in terms of disease response, time to progression and overall survival. The characteristics of these patients are outlined on Table 2. No difference in major prognostic indicators (tumor size at diagnosis, menopausal status, estrogen receptor status and disease free interval) was found between the patients included in and those excluded from the study (X^2 or log-rank p always >0.05. Data not shown).

CA 15-3 variations

Supranormal serum CA 15-3 levels were found in 329 (62.5%) patients at baseline, 258 (49.0%) of which maintained abnormal marker levels at the end of treatment. CA 15-3 determinations were available for 526 patients after 3 months and for 425 patients after 6 months of therapy. At the latter time point, CA 15-3 values were missing for 55 patients and were not

Table 2. Patient characteristics

No. of patients	526
Median age (yr) (range)	57 (27–78)
Premenopausal (no. of patients / %)	149/28.3
Menopausal	377/71.7
Hormone receptor status	
ER +	295 of 483/61.1
PgR +	225 of 459/49.0
Performance Status (ECOG)	
0–1	455/86.5
2–3	71/13.5
Sites of recurrence	
Liver	140/26.6
Lung	195/37.1
Bone	261/49.6
Soft Tissue	169/32.1
Metastatic sites	
1	327/62.2
2	159/30.2
>2	40/7.6
Baseline CA 15-3	
>30 U/ml	329/62.5
≤30 U/ml	197/37.5

determined in the 46 patients who went off protocol due to disease progression or death. Median marker variations (lower–upper quartiles) were: –3.12% (−40.43 to 33.33%) and –19.23% (−58.82 to 19.23%) after 3 and 6 months of therapy, respectively. The calculated areas under the ROC curves to discriminate tumor response were 0.86 (95% confidence interval [CI]: 0.8–0.92; $p < 0.0001$) at 3 months and 0.86 (95% CI: 0.79–0.93; $p < 0.0001$) at 6 months. The optimal cut-off point for marker decrease was –25.42% and –28.48%, respectively. For the subsequent analyses, the –25% cut-off was used to assess a significant CA 15-3 decrease at either 3 or 6 months. The corresponding areas under the curve for tumor progression were 0.8 (95% CI: 0.71–0.9; $p < 0.0001$) and 0.78 (95% CI: 0.64–0.91; $p < 0.01$) and the optimal cut-off points were 25.4% and 22.8%, respectively. The 25% cut-off point was adopted to define a significant marker increase.

Based on changes in marker concentration, the study population was divided into four subsets: (a) Patients with marker levels below the normal threshold of 30 U/l at each time point. Changes in CA 15-3 levels in this group were considered Not Evaluable (CANE group); (b) Patients with a >25% marker decrease over baseline and those with normalization of elevated pretreatment marker levels. This subgroup was defined as CA 15-3 Responder (CAR group); (c) Patients with a >25% marker increase over baseline or those with normal baseline CA 15-3 levels that rose to >30 U/ml during therapy. These patients were classified as CA 15-3 Progressive (CAP group); (d) Patients with elevated baseline marker levels with marker changes occurring within the 25% increase and 25% decrease cut-off points. These patients were grouped into the CA 15-3 No Change group (CANC group).

Patient distribution by marker changes at 3 and 6 months is shown in Table 3.

Table 3. Patient stratification by variation in CA 15-3

Group	Basal CA 15-3	Final CA 15-3	No. of patients
a) At the 3-month time point			
Marker change not evaluable (CANE group)			
CANE	≤30 U/l	≤30 U/l	155
Marker response (CAR Group)			
CAR	>30 U/l	>25% reduction	122
	>30 U/l	≤30 U/l	38
Total			160
No change in marker levels (CANC Group)			
CANC	>30 U/l	<25% increase and <25% reduction	112
Marker progression (CAP Group)			
CAP	>30 U/l	>25% increase	57
	≤ 30 U/l	>30 U/l	42
Total			99
b) At the 6-month time point			
Marker change not evaluable (CANE Group)			
CANE	≤30 U/1	≤30 U/1	133
Marker response (CAR Group)			
CAR	((0 U/1	>25% reduction	123
	>30 U/l	≤30 U/l	52
Total			175
No change in marker levels (CANC Group)			
CANC	>30 U/l	<25% increase and <25% reduction	62
Marker progression (CAP Group)			
CAP	>30 U/l	>25% increase	29
	≤30 U/l	> 30 U/l	26
Total			55

CA 15-3 variations and clinical response

The relationship between clinical response and marker change is described in Figure 1(a, b). Only those patients with elevated baseline serum CA 15-3 were

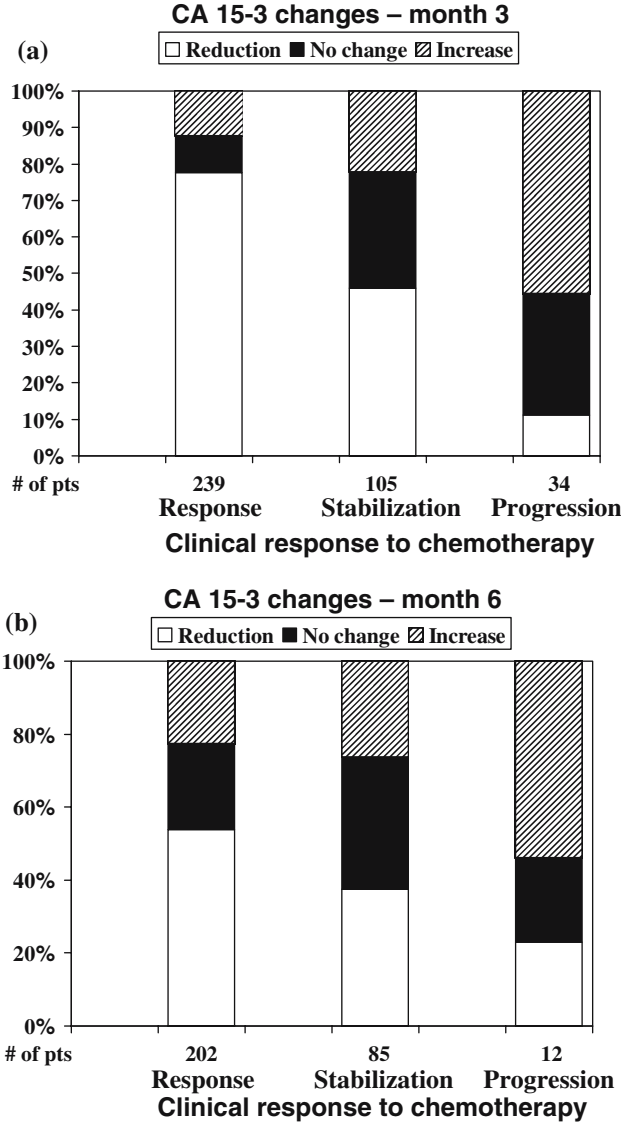

Figure 1. Concordance between serum CA 15-3 changes and clinical response after 3 months (a), and 6 months (b), of therapy in patients with elevated baseline marker values. Data are expressed as the percentage of each respective response category.

considered. A general concordance between these two variables was evident. Patients with a clinical response after treatment showed a marker diminution more frequently than those with progressive disease. Patients with disease stabilization displayed an intermediate pattern of marker changes. Several discrepancies were observed, however. An increase in CA 15-3 values (false positive) was found in 15.2% and 23.7% of patients at 3 and 6 months, respectively. This subset was classified as responders or with disease stabilization to chemotherapy according to the UICC criteria. In contrast, a marker response to chemotherapy (false negative) was found in 44.4% and 46.2% of progressing patients at 3 and 6 months, respectively. Sensitivity and specificity of changes in CA 15-3 levels were 84.8% and 55.6%, respectively, after 3 months and 76.3% and 53.8%, respectively, after 6 months of therapy.

Disease response rates in the CANE group at 3 and 6 months were 64.6% and 71%, respectively, and were comparable with the corresponding response rates obtained in the other groups pooled together at 3 and 6 months (63.2% and 67.3%, respectively). The proportion of patients classified by clinical response into the CANE group was 28.6% and 30.8% in patients obtaining disease response, 27.9% and 28.4% in those with stabilization, and 25.7% and 20.3% in those progressing after 3 and 6 months of therapy, respectively.

CA 15-3 and time to progression

By the end of June 2001, 362 (68.8%) patients had progressed and 164 did not progress or were lost to disease progression (22 patients). The median time to progression for patients stratified by response to therapy was 13.0 months for responding patients and 9.3 months for those with disease stabilization. At 3 months the median time to progression was 13.3 months in not evaluable patients (CANE), 10.8 months in those with marker decrease (CAR), 9.9 months in those with no change in marker (CANC), and 9.9 months in those with increased marker levels (CAP) (overall $p < 0.05$). The corresponding figures at 6 months were 15.3, 11.7, 9.6, and 8.6 months, respectively (overall $p < 0.001$) (Figure 2). In patients obtaining a clinical benefit (i.e. those with disease response or stabilization), the median time to progression was 13.7 months in the CANE group, 11.0 months in the CAR group, 10.4 months in the CANC group, and 10.5 months in the CAP group at the 3-month time point (overall $p < 0.03$), whereas the corresponding figures at 6 months were 14.7, 12.0, 10.3, and 8.8 months, respectively (overall $p < 0.001$).

Multivariate survival analysis according to the Cox model (Table 4, panel a) confirmed CA 15-3 variation at 6 months, performance status, estrogen receptor status of the primary tumor, menopausal status, the presence of liver metastases, and clinical response as independent prognostic indicators for time to progression. Patient age, and lung, bone and soft tissue as predominant metastatic sites failed to enter the model.

CA 15-3 and survival

At the time of data computation, 331 of 526 patients (62.9%) had died; the median follow-up of surviving patients was 23.3 months. Patients with a >50% tumor shrinkage survived longer than those with stable disease or tumor progression. The median survival was: 31.9, 26.9, and 11.9 months ($p < 0.001$), respectively.

Patients with normal baseline CA 15-3 levels showed a longer survival time than those with abnormal marker values (median 40.5 months vs. 28.1 months; $p < 0.001$). The median survival of patients stratified by marker changes at month 3 was 42.2, 28.9, 28.2, and 26.3 months for CANE, CAR, CANC, and CAP, respectively ($p < 0.001$). The corresponding figures at 6 months were 42.3, 29.7, 28.5, 24.8 months, respectively ($p < 0.002$) (Figure 3).

Similar results were obtained in the subset of patients attaining a clinical benefit. The median survival was 41.9, 29.2, 28.1, and 28.2 months in the CANE, CAR,

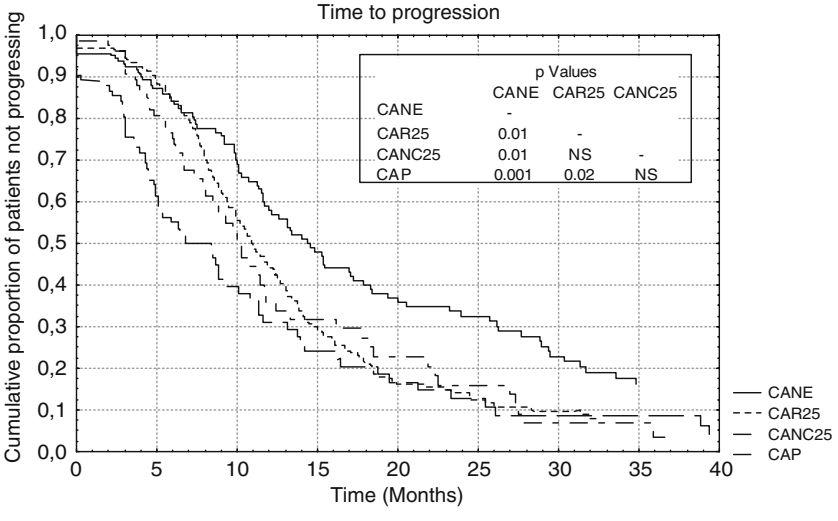

Figure 2. Time to progression curves for patients stratified by variation in serum CA 15-3 levels after 6 months of chemotherapy.

Table 4. Multivariate survival analyses according to the Cox model

Variable	Hazard Ratio	[95% CI] HR	*p*-value
a) *Time to progression*			
ER status at diagnosis	0.993	0.989–0.997	0.05
Performance status	1.137	1.011–1.263	<0.05
Menopausal status	0.842	0.828–0.856	<0.01
Liver metastasis	1.589	1.355–1.823	<0.0001
Clinical response	0.478	0.284–0.672	<0.0001
CA 15-3 changes*	0.991	0.983–0.999	<0.03
b) *Overall survival*			
ER status at diagnosis	0.988	0.977–0.999	0.05
Performance status	1.354	1.214–1.494	<0.001
Menopausal status	0.780	0.640–0.920	<0.001
Lung metastasis	1.251	1.031–1.471	<0.05
Liver metastasis	2.058	1.818–2.298	<0.0001
Clinical response	0.658	0.474–0.842	<0.0001
CA 15-3 changes*	0.997	0.995–0.999	<0.01

Variables failing to enter the model: patient age; bone and soft tissue as predominant metastatic sites.
* At month 6.

CANC, and CAP groups at 3 months ($p < 0.01$) and 42.9, 29.7, 28.1, and 23.2 months at 6 months, respectively ($p < 0.001$).

When survival computation was performed after the 6-month landmark point, the median survival was 36.3 months in the CANE, 23.7 months in the CAR, 22.8 months in the CANC and 19.4 months in the CAP subgroups ($p < 0.002$). Mortality rates within 6 months over the 3-month time point for the 4 patient subgroups were: 4.0%, 5.6%, 10.7%, and 11.6%, respectively ($p < 0.05$), whereas the corresponding figures over the 6-month time point were: 9.1%, 11.0%, 11.5%, and 29.6%, respectively ($p < 0.001$).

Multivariate survival analysis according to the Cox model (Table 4, panel b) showed that CA 15-3 variation at month 6, performance status, estrogen receptor positivity of the primary tumor, menopausal status, presence of visceral metastases, and clinical response were independent prognostic indicators. Patient age, and bone and soft tissue as dominant metastatic sites failed to enter the model.

Discussion

In our study, levels of the tumor marker CA 15-3 were measured and disease response was assessed in a large number of metastatic breast cancer patients followed prospectively during first-line chemotherapy. The clinical response rate to anthracycline-based first-line chemotherapy was similar to that reported elsewhere [29–31] and, as expected, correlated significantly with time to progression and overall survival. A general correlation was observed between clinical response and variation in serum CA 15-3 levels, thus confirming previous data [14–19]. However, the marker response in the present series paralleled the disease response is only about 50–60% of patients.

We have identified three CA 15-3 patterns with different prognostic significance. Patients with CA 15-3 levels within the normal range before and after treatment presented a more indolent form of the disease, with the longest time to progression and survival, whereas those with increased CA 15-3 had an aggressive treatment-resistant disease, with the worst time to progression and survival. An intermediate prognostic behavior was found in those obtaining a reduction in CA 15-3 or no change. These figures were confirmed when the survival analysis was performed at the 6-month landmark point, thus reducing the inherent bias of assessing survival as a function of marker response. Moreover, relative changes in CA 15-3 at 3 and 6 months were sufficient to significantly predict prognosis over the next few months, since the chance of dieing of disease within the succeeding 6 months was twice as high at the 3-month time point and three times as high at the

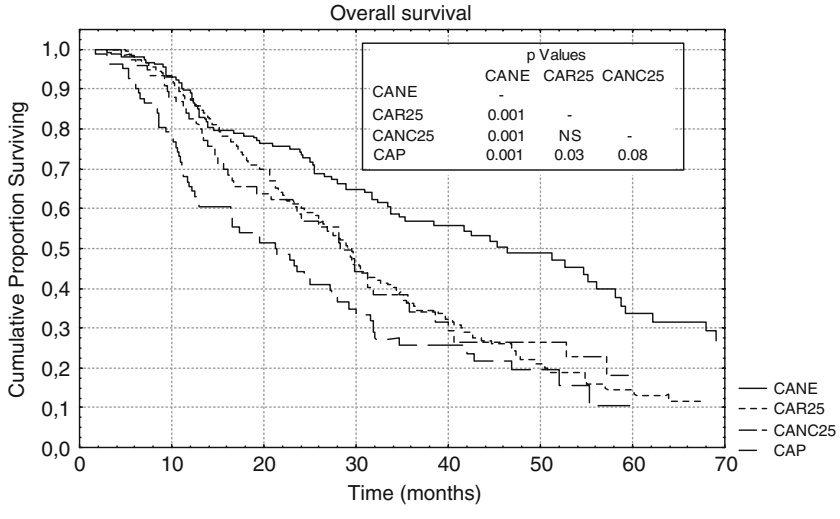

Figure 3. Overall survival curves for patients stratified by variation in serum CA 15-3 levels after 6 months of treatment.

6-month time point for patients in the CAP group than for their counterparts.

Interestingly, the prognostic significance of the CA 15-3 patterns persisted in the univariate analysis in the patient subset that obtained a clinical benefit from the therapy (i.e. patients with disease response or stabilization) and after adjusting for disease response and major prognostic parameters in the multivariate analysis. These data suggest that measurement of CA 15-3 may offer additional and independent prognostic information.

In this patient series, we did not observe the transient CA 15-3 rise usually found shortly after the initiation of effective treatments [32]. Thus, marker measurement at 3 and 6 months might have avoided false interpretation of early marker assessment.

This study, based on a large dataset of patients treated at five different institutions, while confirming the good sensitivity of CA 15-3 in the metastatic setting and the good correlation between marker changes and tumor response reported elsewhere [11,14,32], provides us with at least two novel findings. The one is that CA 15-3 variation during first-line chemotherapy with anthracyclines is an independent prognostic factor to be taken together with other parameters (e.g. biological characterization of the primary tumor and clinical response to therapy) in the management of metastatic breast cancer patients. The other finding is that marker levels below the cut-off should not be considered a false negative (i.e. a meaningless value), because patients with persistently below threshold CA 15-3 values had a longer time to progression and survival, and those with a negative baseline marker that became positive during therapy had a more aggressive tumor. These data suggest that monitoring of serum CA 15-3 should be continued during therapy, even in the absence of supranormal levels at presentation.

That these findings are not robust enough to radically change the clinical approach to managing these patients warrants further study in prospective trials. Studies using marker values as the sole criterion for treatment choice are difficult to perform in practice, and any observation in this sense is welcome. As concerns the discordant clinical/marker results (i.e. 20%–40% of our study population), while decreased marker levels in the presence of clinical progression may be a pitfall of marker evaluation, an increase in marker values, despite disease response or disease stabilization, suggests poor outcome. The implication is that patients showing a clinical benefit from treatment but rising CA 15-3 levels require more careful restaging and stricter than usual follow-up. From the patient's point of view, having a simple tool to predict overall survival would also be helpful.

One limitation to our study was that the CA 15-3 determinations were performed by 10 different laboratories using four different commercial kits. So to avoid inter-laboratory variation, blood samples from the same patient were analyzed by the same laboratory. In addition, the multicentric design of our study better reflected general practice in oncology.

In conclusion, serum CA 15-3 determination is an easily available low-cost repeatable test that can provide additional clinical information for assessing tumor response in advanced breast cancer patients undergoing chemotherapy. Three consecutive marker measurements performed every 3 months allowed the definition of three patient subsets with different survival prospects. Although measuring serum CA 15-3 levels cannot be used as the sole criterion for clinical decision-making, it may aid in differentiating between patients very likely to benefit from systemic antineoplastic treatments from those who are not.

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