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Prognostic Value in Predicting Overall Survival of Two Mucinous Markers: CA 15-3 and CA 125 in Breast Cancer Patients at First Relapse of Disease

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The role of circulating tumour markers in providing prognostic information has been scarcely studied. We evaluated the prognostic significance of two mucinous markers: CA 15-3 and CA 125 in 115 breast cancer patients at first recurrence of disease. At diagnosis of advanced disease bone involvement was found in 64 patients, lung in 57, skin lymph nodes in 21, liver in 20, and brain in 5. Patients were recruited and treated in the same institution with conventional chemo- or endocrine therapy. The follow-up ranged from 3 to 54+ months (median 35). Serum samples were drawn at first recurrence of disease before the start of any endocrine and/or chemotherapy. Patients with CA 15-3 <30 U/ml survived significantly longer than those with CA 15-3 >30 U/ml (median 50+ versus 26 months, $P<0.02$). Similarly, overall survival of patients with CA 125 <35 U/ml was significantly higher in comparison with patients with CA 125 >35 U/ml (median 34.5 versus 18.5 months, $P<0.001$). CA 125, but not CA 15-3, maintained its prognostic value in the subgroup of patients with visceral metastases. Both markers were found to be independent prognostic variables in multivariate analysis according to Cox's model. CA 15-3 and CA 125 appeared to be powerful prognostic indicators, in addition to visceral metastases, in patients with advanced breast cancer.
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INTRODUCTION

CA 15-3 is the most commonly used circulating tumour marker in breast cancer patients [1]. It is a breast cancer-associated antigen that is defined by its reaction with monoclonal antibodies 115D8 and DF3 [2]. CA 15-3 determination is particularly useful in evaluating recurrence of disease and response to treatment [3]. However, its prognostic role in predicting overall survival has been scarcely studied. Colomer and associates [4] showed that patients with advanced breast cancer and elevated CA 15-3 levels had lower median survival than those with non-elevated CA 15-3. However, overall survival in this series of patients was measured from the time when serum samples were obtained and not from the first appearance of metastatic disease.

CA 125, defined by monoclonal antibody OC125, is commonly used in the monitoring of epithelial ovarian cancers [5], but its serum level can be increased in many other malignancies including those of the pancreas, lung, stomach, colon, endometrium [6]. The sensitivity of CA 125 in advanced breast cancer patients was recently found to be higher than previously reported [7], even though its clinical usefulness has been questioned [8].

In some reports, increased serum CA 125 levels have been found significantly related to poor survival in patients with ovarian cancer [9], non-small cell lung cancer [10], cervical carcinoma [11].

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The purpose of this study was to investigate the prognostic significance of two mucinous markers: CA 15-3 and CA 125 in breast cancer patients at first recurrence of disease.

MATERIALS AND METHODS

Patients

From October 1988 to January 1993, 115 consecutive patients with advanced breast cancer entered the study. First diagnosis, mastectomy and follow-up before recurrence were performed in different institutions. However, from the time of first relapse onwards, all patients were treated and followed at the Servizio di Oncologia Medica, Ospedale San Luigi Gonzaga, Orbassano (Torino, Italy). Recurrences were classified as visceral (brain, liver, lung), bone or soft tissue. Sites of recurrence were documented by physical examination, X-rays and/or scans. Only the first site of metastasis, either locoregional or distant, was recorded and evaluated. When more than one site was concomitantly involved, patients were classified according to the dominant site of metastasis. The hierarchy of metastasis with progressively worse prognosis was assumed to be soft tissue, bone and visceral. The primary treatment was mastectomy or quadrantectomy with axillary node dissection. Patients submitted to quadrantectomy received radiation therapy. Adjuvant treatment was administered in patients with positive nodes and/or negative steroid hormone receptors, and consisted of standard CMF (cyclophosphamide, methotrexate, fluorouracil) chemotherapy in premenopausal patients and in postmenopausal ones with negative steroid hormone receptors and endocrine therapy (tamoxifen) in postmenopausal patients with hormone-depen-

dent tumours. Therapy for limited, locoregional metastasis consisted of metastasectomy followed by radiotherapy. Postmenopausal patients with either bone or soft tissue metastases, the latter not suitable for radical surgery, and oestrogen receptor (ER) and/or progesterone receptor (PgR)-positive primary tumour, received endocrine therapy (tamoxifen, aminoglutetimide, medroxyprogesterone acetate). Patients in premenopause and/or with visceral metastases received anthracycline-based chemotherapy (FEC: fluorouracil, epirubicin, cyclophosphamide or epirubicin alone, at 120 mg/m^2) as first-line treatment, followed by endocrine therapy if primary tumours were ER and/or PgR-positive.

Marker assays

CA 15-3 and CA 125 serum levels were evaluated at first recurrence of disease before the start of any endocrine or cytotoxic therapy. Both markers were measured in the same laboratory using two step immunoradiometric assays (Centocor, Malvern, U.S.A.). Serum samples were frozen at −70° if not analysed within 24 h. The lowest detection level for both markers was 5 U/ml. CA 15-3 and CA 125 tests had intra-assay variabilities of 3.8 and 4.8%, respectively and inter-assay variabilities of 6.5 and 7.2%, respectively. The upper normal concentrations were 30 and 35 U/ml, respectively.

Statistical analysis

Differences between proportions were assessed with χ^2 test with Yates correction. Overall survival was measured from the time of first recurrence. Univariate analysis was performed using the method of Kaplan and Meier [12], and compared using the log rank test [13]. Multivariate analysis was assessed using the stepwise Cox regression model [14]. All tests were performed at the 0.05 level of significance. Statistical computations were made using SPSS software [15].

RESULTS

Patient characteristics are shown in Table 1. At diagnosis of breast cancer, 111 (97%) patients had stage I or II disease, and only 4 (4%) patients had concomitantly metastatic disease. Receptor status was recorded for 68 tumours: 49 (72%) had ER-positive (≥10 fmol/mg) tumours and 35 (51%) had PgR-positive tumours (≥20 fmol/mg). 48 (42%) patients received adjuvant endocrine therapy or chemotherapy. 52 (45%) patients had recurrence within 2 years after mastectomy.

Table 1. Patients' characteristics

	No. of patients
Total no. of patients	115
Age (years)	
Median	56
Range	30–81
Menopausal status	
Premenopausal	35
Postmenopausal	80
PS ECOG	
0–1	101
2–3	14
Metastatic sites	
Skin/Lymph nodes	21
Bone	64
Lung	57
Pleural effusions	19
Brain	5
Number of sites	
One site	75
Two or more	40

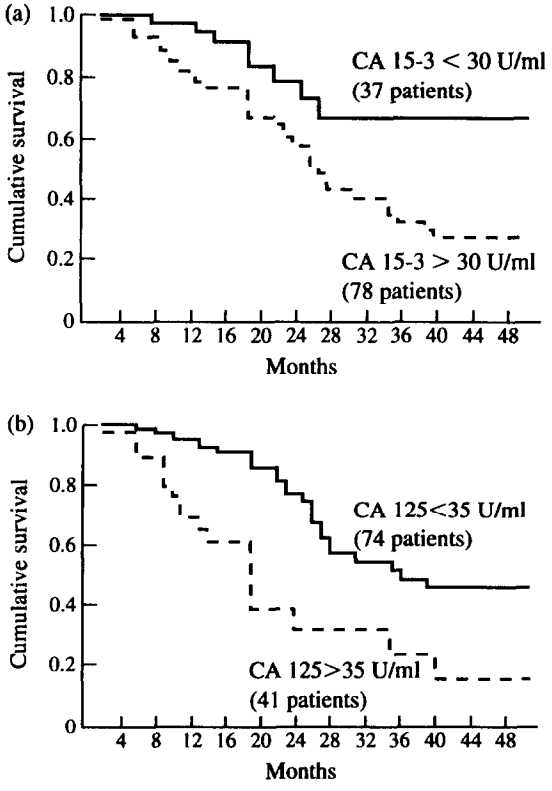

Figure 1. Survival curves of advanced breast cancer patients according to their marker levels at the time of first relapse. (a) CA 15-3 (log rank test, $P < 0.02$). (b) CA 125 (log rank test, $P < 0.001$).

64 (56%) patients had initial recurrence in bone, 57 (50%) in the lung, 20 (17%) in the liver, and 21 (18%) in soft tissue. 19 (17%) patients presented with pleural effusions, none had ascites. Approximately one-third of patients had simultaneous recurrence in more than one metastatic site. The median time of follow-up from first recurrence was 35 months (range 3–54+). The last day of follow-up was 30 September 1993. 56 of the 115 evaluable patients died.

Marker analyses

The overall sensitivities of CA 15-3 and CA 125 were 68 and 36%, respectively ($P<0.001$). The concomitant measurement of both markers did not improve the sensitivity of CA 15-3 alone. Patients with visceral metastases as dominant site of recurrence had significantly more abnormal CA 15-3 (86 versus 33%, $P<0.001$) and CA 125 values (53 versus 6%, $P<0.001$) than patients with bone and soft tissue involvement. In the subgroup of patients with lung metastases, the sensitivities of CA 15-3 and CA 125 were 88 and 66% ($P<0.02$), while the specificities (considering the patients without lung involvement as controls) were 44 and 77%, respectively ($P<0.001$). 18 of 19 patients (95%) with pleural effusions had CA 15-3 values above the normal range, and 17 of 19 (89%) had abnormal levels of CA 125.

Table 2. Multivariate analysis according to Cox's model

Variable	Coefficient	S.E.	χ^2	*P* value
Visceral metastases	+1.3218	0.3464	16.449	<0.0001
CA 15–3	+0.7762	0.3652	5.093	<0.03
CA 125	+1.1089	0.3293	7.714	<0.001

Univariate survival analysis

Patients with CA 15-3 within the normal range survived significantly longer than the ones with elevated serum levels (median survival 50+ versus 26 months, $P<0.02$, Figure 1(a)). Similarly, patients with normal levels of CA 125 had a better survival than those with high levels (median survival 34.5 versus 18.5 months, $P<0.001$, Figure 1(b)). Worse survival was found in patients with visceral metastases (median 26 months) in comparison with those with bone and soft tissue involvement (median 50+ months, $P<0.01$). In the subgroup of patients with visceral metastases, CA 125, but not CA 15-3, maintained its prognostic value (median survival 30.5 versus 18 months, $P<0.003$).

Multivariate survival analysis

Table 2 shows the results of a multivariate analysis of the potential prognostic factors. CA 125, CA 15-3, and visceral metastases were found to be independent prognostic factors, whereas age, performance status and bone–soft tissue involvement did not enter the model.

DISCUSSION

The present study confirms the relatively high sensitivity of CA 15-3 in advanced breast cancer. CA 125 was found to be moderately sensitive, but more specific than CA 15-3 in the subgroup of patients with lung involvement. The combination CA 15-3 plus CA 125 did not enhance the sensitivity of CA 15-3 alone.

The prevalence of elevated levels of both markers varied with the site of metastasis. Patients with visceral involvement had more frequent elevations than patients with bone and soft tissue involvement. The highest sensitivity of both markers was found in patients with pleural effusion.

In this series of patients, uniformly treated and followed from the diagnosis of metastatic disease in the same institution, either high levels of CA 15-3 or supranormal values of CA 125 were found to significantly correlate with poor survival in univariate analysis. Within patients with visceral metastases, elevated CA 125 levels were associated with decreased survival, suggesting that its prognostic significance may be independent from the relationship between marker elevation and site of metastasis. In this subset of patients, CA 15-3 was not shown to be a prognostic factor, probably due to the low number of patients with serum levels within the normal range.

Both markers were found to be independent prognostic variables in predicting overall survival in multivariate analysis.

TNM stage, steroid hormone receptor status, disease-free interval and dominant site of first metastases are the widely recognised prognostic indices for advanced breast cancer patients [16, 17]. Except for the site of first recurrence, all of these refer to retrospective information on primary tumour.

Circulating levels of CA 15-3 and CA 125, determined at first recurrence of disease, represent a powerful additional prognostic factor. This could be ascribed to the correlation of marker levels with the extent of metastatic disease [4], or may reflect the state of cell differentiation and aggressiveness of the tumour [1].

Since an estimation of tumour load in metastatic disease is generally difficult in practice, the use of tumour markers may have some usefulness in this respect. The observed differences in the prevalence of elevated values between different sites suggest a relationship with patterns of tumour growth and spread. The finding of the highest values in patients with pleural effusion would, however, not quite fit with the general experience that such patients do not necessarily have the worst prognosis, if treated properly, but larger studies may clarify this situation.

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