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Report

Evaluation of serum tumor markers in patients with advanced or recurrent breast cancer

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Summary

Serum CA15-3, CEA, and BCA225 concentrations were determined in 98 patients with advanced or recurrent breast cancer in an attempt to correlate elevation with clinical status. The rate of serum positivity was 68.4% (67/98), 55.1% (54/98), and 43.9% (43/98) for CA15-3, CEA, and BCA225, respectively. After a 4 weeks-interval, a 20% change of tumor marker concentration from the preceding assay correlated significantly with clinical findings. Significant elevation was predictive of new recurrence or tumor regrowth after complete remission, especially in patients with bone metastasis. The 20% change in concentration at 4 weeks was also useful in patients with tumor marker concentrations persistently beneath the cut-off level for positive. Serological evaluation of tumor markers in patients with advanced or recurrent breast cancer should seek to document 20% changes over a 4 week interval.

Introduction

Although there are multi-modal therapies available for advanced or recurrent breast cancer, the degree and duration of response vary widely from patient to patient. It is not uncommon for patients who respond to first line therapy to respond to second-line therapy after regrowth of tumor. Therefore, the reliable determination of disease activity has been a priority in breast cancer clinics [1]. Reliable evaluation of postoperative patients in long-term follow-up is also important for earlier detection of recurrence [1]. However, the clinical evaluation is often unreliable, especially in patients with bone or pleural metastases [2].

CA15-3 is a high-molecular-weight, carbohydrate breast cancer-associated antigen. Higher serum levels are found in patients with multiple sites of metastases and bone metastases [2–8]. Carcinoembryonic antigen (CEA) is an oncofetal glycoprotein discovered in patients with adenocarcinoma of the colon. This serum glycoprotein is commonly used as a tumor marker for not only colorectal cancer but also breast cancer [2, 5, 8]. BCA225 is also a gly-

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coprotein identified in cells and spent medium of clone 11 T47D breast carcinoma cells by the three monoclonal antibodies CU18, CU26, and CU46 [9, 10]. Although these serum markers have little value for the diagnosis of primary breast cancer, they are useful for monitoring the clinical course for recurrence or progression of breast cancer [4–6]. However, few studies have sought to determine specific criteria for the use of tumor markers as an adjunct to clinical assessments [2, 11].

In this paper, serum CA15-3, CEA, and BCA225 were measured every 4 weeks in 98 patients with advanced or recurrent breast cancer, and the relation between clinical and serological findings was analyzed. Also, the feasibility of predicting tumor recurrence from serological evaluation was also examined in patients who had recurrence during postoperative follow-up periods or regrowth after complete remission.

Subjects and method

Patients

Subjects consisted of 98 patients treated between July 1991 and December 1992 with measurable and/or evaluable foci of advanced or recurrent breast cancer. There were 51 soft tissue, 56 bone, 34 lung or pleura, 13 liver, and 5 brain metastases. Fifty-six patients had a single focus of disease. Chemoendocrine therapy administered during the study period included 5-fluorouracil (5FU) + medroxyprogesterone acetate (MPA) in 30 patients, cyclophosphamide (CPA) + Adriamycin (ADM) + 5FU in 38 patients, CPA + Methotrexate (MTX) + 5FU in 21 patients, and other drug therapies in 32 patients. Thirty-eight patients received multi-modal chemoendocrine therapies. Thirteen patients received radiotherapy in addition to chemoendocrine therapy. Surgical resection was performed in 5 patients. The mean follow-up period was 12.9 months.

Tumor markers

Serum CA15-3, CEA, and BCA225 concentrations were measured once every 4 weeks after recurrence in each subject. The markers were also measured once every 3 to 6 months during the postoperative follow-up period and immediately before the beginning of each cycle of chemotherapy. Measurements were performed 2 weeks or more after the end of a cycle of radiotherapy.

Serum CA15-3, CEA, and BCA225 concentrations were assayed using enzyme immunoassay (EIA) (Centcore Co., Inc., USA), radioimmunoassay (RIA) (Sanyo Kasei Kogyo Inc., Japan), and EIA (Kuraray Co., Inc., Japan) commercial kits. The cut-off levels for positive were set as 30 U/ml for CA15-3, 5.0 ng/ml for CEA, and 160 U/ml for BCA225 as previously described [3, 8, 9].

Clinical evaluation

According to the recommendations of the Japanese Breast Cancer Society for therapeutic evaluation in patients with advanced or recurrent breast cancer, clinical evaluation was performed once every 4 weeks. Ultrasonography, computed tomography, bone radiographs, and nuclear imaging studies were used in some cases. Measurable foci were evaluated as follows: a 50% or more decrease in dimension was considered response (R) to therapy, a decrease of less than 50% and increase of less than 25% was considered no change (NC), and a 25 percent or more increase was considered progressive disease (PD). Because the present study was designed to examine the utility of tumor markers, the duration of therapeutic effect was not considered. There were 761 points in which both serological and clinical evaluation were performed simultaneously.

Serological evaluation

The percent decrease or increase from the preceding measurement was used to separate R, NC, and PD, respectively. Interpolated values for 4 weeks intervals were used when the preceding assay was performed more than 4 weeks before, especially in postoperative follow-up periods. The results of the serological evaluation were tentatively set at 1% to

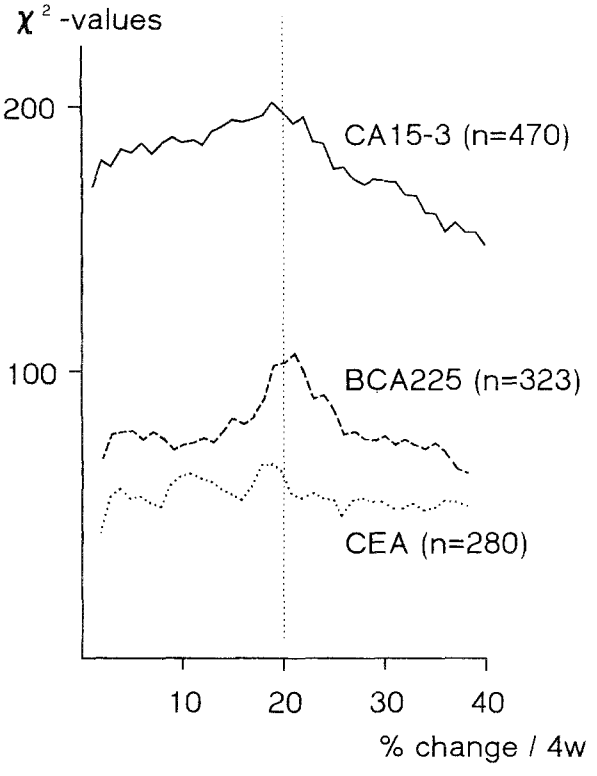

Fig. 1. Correlation between clinical and serological evaluation at positive assay points: A 19% interval change of CA15-3 concentration at 4 weeks had the highest correlation with clinical assessment (Chi-square value = 203.942, n = 470). When the criterion for serological evaluation was 20%, the correlation was still statistically significant (201.615, n = 470). Although CEA (Chi-square value = 64.284, n = 280) and BCA225 (Chi-square value = 102.236, n = 323) concentrations also showed significant correlation with an approximately 20% interval changes, the correlation was weaker than with CA15-3.

40% and corresponding correlations with clinical findings were analyzed by the Chi-square test.

Results

Tumor marker positive rates

The rates of positivity for CA15-3, CEA, and BCA225 were 68.4% (67/98), 55.1% (54/98), and 43.9% (43/98), respectively. The difference of positivity between CA15-3 and BCA225 was statistically significant ($p < 0.01$) by Rayn's multiple comparison. At least one of the three tumor markers was positive in 80.6% (79/98) of cases. On the other hand, there were 10 cases positive for only one tumor marker.

The rates of positivity of the various tumor markers at the beginning of treatment were 60.9% (14/23), 76.0% (19/25), 100% (6/6), 100% (1/1), 100% (1/1), and 95.0% (38/42) in soft tissue, bone, lung and/or pleura, liver, brain, and multiple foci of metastasis, respectively.

Serological evaluation of tumor marker positive points

Among the positive assay points of CA15-3, a 19% change per 4 week interval showed the highest correlation with clinical findings (Chi-square value = 203.942, n = 470: Fig. 1). At a 20% per 4 week interval, the correlation was still significant ($P < 0.01$) and the Chi-square value was high (201.615, n = 470), as shown in Table 1.

Although the highest peaks of x^2 values were at 19% and 21% changes for CEA and BCA225, respectively, both the markers still showed significant correlations with clinical findings at 20% change in each positive assay points. However, the correlation of CEA and BCA225 with clinical findings was weaker than that of CA15-3 (Fig. 1).

Serological evaluation of tumor marker negative points

There were 291, 438, and 489 points showing lower values than cut-off levels of CA15-3, BCA225 and

Table 1. Correlation between clinical and serological evaluation. Serological evaluation by assessment of a 20% change per 4 weeks correlated well with clinical evaluation

Clinical evaluation	Changes of CA15-3 values (%/4wk)			
	≤ −20	−20 to 20	20 ≤	total
Response	24	22	1	47
No change	23	201	51	275
Progress	1	49	98	148
Total	48	272	150	470

x^2 values = 201.615 ($p < 0.01$)

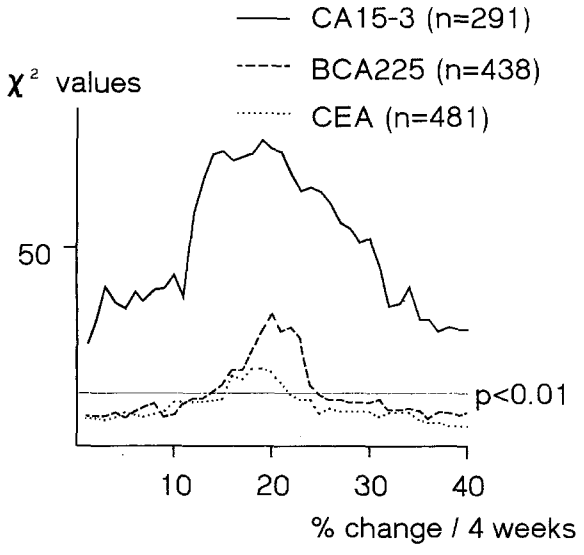

Fig. 2. Correlation between clinical and serological evaluation at negative assay points: A 19% interval change of CA15-3 concentration at 4 weeks also showed the highest correlation with clinical assessment (Chi-square value = 74.374, n = 291: Fig. 2). When the criterion percentage was 20%, the correlation was still significant (73.968, n = 291). Although CEA and BCA225 concentrations showed significant correlation around at approximately 20% interval changes, the correlation was weaker than with CA15–3.

CEA, respectively. Therefore, they were analyzed independently from pre-described positive points. A 19% change among the negative assay points of CA15-3 showed the highest correlation with clinical findings (Chi-square value = 74.374, n = 291: Fig. 2). The correlation was equally high when the criterion for significance was set at 20% change (Chi-square value = 73.968, n = 291). Although both the CEA and BCA225 also showed a significant correlation with clinical findings with changes of a approximately 20%, the correlation was weaker than that of CA15-3 (Fig. 2).

Prediction of recurrence or relapse

There were 34 clinically-diagnosed episodes of recurrence or relapse during the study period. Among them, 14 cases had increased tumor marker concentrations above the cut-off level prior to the recognition of clinical recurrence. While 11 cases had positive tumor markers after or at the same time as clinical recurrence, and 9 maintained stable tumor marker concentrations even after recurrence. Among the former 11, 4 were predictable by the criterion of a 20% increase per 4 weeks interval (Fig. 3). Thus prediction of tumor recurrence based on serological data was possible in 18 cases (14, 8, and 7 cases by CA15-3, CEA, and BCA225, respectively). The lead time, which is defined as the time of serological prediction using a 20% change per 4 weeks prior to clinical determination, was 4.1 ± 1.0 months for CA15-3, 3.2 ± 0.8 months for CEA, and 3.6 ± 1.5 months for BCA225. Twelve of these 18 cases had bone metastases.

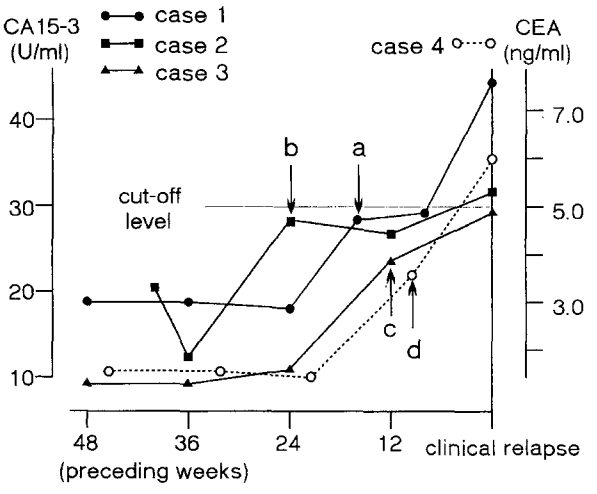

Fig. 3. Prediction of relapse by assessment of 20% change at 4 weeks: Four of 20 cases could have been predicted by the criterion of a 20% increase at 4 weeks. Case 1 with liver metastasis, case 2 with bone metastasis, case 3 with bone metastasis and case 4 with local recurrence, could have been predicted in the preceding 14 weeks (28.5% increase: arrow a), 24 weeks (44% increase: arrow b), 12 weeks (38.5%: arrow c), and 8 weeks (46% increase: arrow d), respectively, before clinical relapse.

Discussion

Although the highest incidence of positivity in recurrent cases was observed for CA15-3, there were no cases uncommonly with elevated markers excluding CA15-3. Compared to advanced stages of disease, the prevalence of positive serum tumor markers early in the course of breast cancer is very low [2, 5–11]. It is, therefore, assumed that a relatively large number of tumor cells are necessary for

the detection of tumor markers. However, the degree of elevation depended not only on tumor volume but also on other individual issues including the tissue involved [4, 6, 12]. Relative values obtained by comparison with the preceding assay should therefore be emphasized instead of absolute values of tumor marker concentration.

Some investigators have attempted to estimate tumor doubling time by plotting tumor marker concentrations on a semi-logarithmic graph [13]. Others have attempted to assess the efficacy of therapies by plotting tumor marker concentrations before and after treatment [12]. Although these methods are accurate, they are too cumbersome for routine use. Therefore, more accessible but highly reliable criteria for tumor marker assessment have been warranted. Ohkura [12] reported the accuracy of a decreased serum CEA concentration as a prognostic marker for patients with colorectal cancer after chemotherapy. Patients whose serum CEA concentration decreased by more than 50% showed similar survival intervals to those found to be free of tumor by conventional diagnostic imaging.

In the present study, the significance of serological evaluation was analyzed with respect to clinical findings by Chi-square analysis. The highest peaks of Chi-square values were around 20% change in all the tumor markers. This approach is also applicable in cases with tumor marker concentrations below the usual cut-off levels. Therefore, it is convenient with enough reliability in daily breast cancer clinic to use 20% change as an evaluation criterion of serum tumor markers.

Recurrence or regrowth of bone metastasis is often more predictable by measurement of tumor markers than are other types of metastasis because of the difficulty in clinical diagnosis of bone metastasis. Additionally, tumor antigens may be readily released from the cell surface into the blood stream via the bone marrow in patients with bone metastasis. The serological evaluation of tumor markers thus has greater relevance to patients with breast cancer and bone metastasis. Findings suggestive of recurrence with clinical and serological methods were obtained in 11 cases who had positive tumor markers after or at the same time as clinical recurrence. Four of these 11 could be predicted using the criterion of a 20% increase per 4 weeks interval.

The 20% change 4 weeks from the preceding assay also showed a highly significant correlation with clinical assessment in two other markers. It is well known that serum tumor markers often increase due to tumor cell death just after chemotherapy or irradiation. Since these transient elevations decline within 2 weeks, the assessment of tumor markers every 4 weeks can be useful.

References

1. Kobayashi S, Iwase H: Prognostic factors and evaluation of effect in drug therapy of breast cancer. Excepta Medica, International Congress Series 945, 1990, pp 183–190
2. Iwase H, Kobayashi S: Evaluation of effects of breast cancer treatments by serum tumor marker. Jpn J Breast Cancer 7: 356–365, 1992 (in Japanese)
3. Kobayashi S, Iwase H, Karamatsu S, Matsuo K, Masaoka A, Miyagawa T: The clinical value of serum CA15-3 assay postoperatively in breast cancer patients. Jpn J Surg 19: 278–282, 1989
4. Colomer R, Ruibal A, Genolla J, Rubio D, DelCampo JM, Bodi R, Salvador L: Circulating CA15-3 levels in the postsurgical follow-up of breast cancer patients and in non-malignant diseases. Breast Cancer Research and Treatment 13: 123–133, 1989
5. Colomer R, Ruibal A, Salvador L: Circulating tumor marker levels in advanced breast carcinoma correlate with the extent of metastatic disease. Cancer 64: 1674–1681, 1989
6. Gion M, Mione R, Nascimben O, Valsecchi M, Gatti C, Leon A, Bruscagnin G: The tumour associated antigen CA15-3 in primary breast cancer. Evaluation of 667 cases. Br J Cancer 63: 809–813, 1991
7. Duncan JL, Price A, Rogers K: The use of CA15-3 as a serum tumor marker in breast carcinoma. Eur J Surg Oncol 17: 16–19, 1991
8. Dnistrian AM, Schwartz MK, Greenberg EJ, Smith CA, Schwartz DC: CA15-3 and carcinoembryonic antigen in the clinical evaluation of breast cancer. Clinica Chimica Acta 200: 81–94, 1991
9. Mesa-Tejada R, Palakodety RB, Leon JA, Khatcherian AO, Greaton CJ: Immunocytochemical distribution of a breast carcinoma associated glycoprotein identified by monoclonal antibodies. American Journal of Pathology 130: 305–314, 1988
10. Hirohashi S, Watanabe M, Shimosato Y: Monoclonal antibody reactive with the sialyl-sugar residue of a high molecular weight glycoprotein in sera of cancer patient. Jpn J Cancer Res 75: 485–488, 1985
11. Mobus V, Paula J, Beck T, Crombach G, Kreienberg R:

Tumour Marker Courses to assess the efficacy of chemotherapy or hormone therapy in metastasising breast cancer. Geburtsh u Frauenheilk 53: 24–29, 1993 (in German)

12. Ohkura H, Sugano Y, Shimada Y, Saitou D, Shirao K, Okazaki N, Okada S, Yoshimori M: Evaluation of cancer treatment by serum markers. J Clin Surg 47: 6231–628, 1992 (in Japanese)
13. Staab HJ: Slope analysis of the postoperative CEA time course and possible application as an aid in diagnosis of disease progression in gastrointestinal cancer. Am J Surg 136: 322–327, 1978