J Cancer Res Clin Oncol (1984) 108:341–344

Journal of Cancer Research and Clinical Oncology

Metastatic Breast Cancer with Constantly Low CEA Blood Levels

A Subgroup with Unfavorable Prognosis?

G. Krieger[1], H.-E. Wander[1], M. Kneba[1], M. Prangen[1], G. Bandlow[2], and G. A. Nagel[1]

[1] Abteilung für Hämatologie/Onkologie, Medizinische Universitätsklinik Göttingen, Robert-Koch-Straße 40, D-3400 Göttingen, Federal Republic of Germany
[2] Zentrum für Hygiene und Humangenetik, Universität Göttingen, D-3400 Göttingen, Federal Republic of Germany

Summary. The capability of breast cancer to secrete CEA might have biological significance. In 105 patients with metastatic breast cancer serial CEA determinations and clinical follow-up data were available during progression of disease up to death. In this series, 39 patients (37%) had constantly low CEA levels (< 10 ng/ml), whereas 66 patients (63%) showed CEA values exceeding 10 ng/ml with progression. The patients with low CEA levels had significantly shorter median survival times ($P = 0.001$) after mastectomy (39 versus 65 months) and after recurrence (18 versus 28 months) than the patients with high CEA levels. This difference was due first to a poor-risk group of 13 patients with rapidly disseminating tumors, very short survival (< 12 months), and low CEA levels. Secondly, there were more patients with pulmonary involvement and unfavorable prognosis and fewer patients with osseous metastases and long survival in the low-CEA group.

In conclusion, there might be a subtype of breast cancer with rapid progression and low CEA secretion. This clinical observation has to be confirmed by histological grading and CEA staining of these tumors.

Key words: CEA – Breast cancer – Prognosis

Introduction

CEA blood levels might have prognostic significance in metastatic breast cancer (mbc). It has been reported that high CEA levels predict unfavorable prognosis and poor response to chemotherapy (Tormey and Waalkes 1978; Bezwoda et al. 1981). However, CEA levels are positively correlated with more advanced disease, with large tumor burden, and probably with liver involvement (Tormey et al. 1977), and no further investigation was conducted as to whether the CEA value was an independent prognostic variable.

The present longitudinal study allows another approach to the prognostic implications of low and high CEA levels in mbc. Since CEA values were continuously monitored during progression of disease until death the patients could be divided into a group with constantly low CEA levels (< 10 ng/ml) and a group of patients reaching high CEA levels (> 10 ng/ml) during disease. Then the two groups were compared with regard to prognostic factors, response to chemotherapy, and survival after mastectomy and after recurrence. Furthermore, the clinical data were analyzed to find out whether the patients with constantly low CEA levels died with low tumor burden involving unfavorable sites or whether there was a subgroup of patients having large tumor burden with low secretory capability for CEA.

Offprint requests to: G. Krieger

Abbreviation: Metastatic breast cancer – mbc

Patients and Methods

Patients

A nonselected series of 157 patients with metastatic breast cancer (mbc) scheduled to be treated with chemotherapy at the Department of Oncology, Goettingen University Hospital, entered this study from 1 April 1979 to 31 June 1981. The cut-off date for the observation period was 1 April 1984. Seven patients were lost to follow-up. Of the remaining 150 patients, 106 died during the observation period and their data were evaluated for this study. These patients met the following criteria:

Inoperable, recurrent, or metastatic carcinoma of the breast; Clinical examinations and CEA determinations 1- to 3-monthly during follow-up until death; Sufficient data available on treatment of the primary tumor (mastectomy) and subsequent clinical course.

The following data were recorded on entry to the study according to the definitions of the EORTC (Rozencweig and Heuson 1975): age, menopausal status, disease-free interval, number of previous therapies, number of involved sites, dominant site of lesions, performance status. If possible, the histology and the lymph node status at mastectomy and the hormone receptor status of primary or secondary lesions were recorded. Estrogen receptor values > 10 fmol/mg cytosol protein and/or progesterone receptor values > 20 fmol/mg were classified as receptor-positive.

Clinical Examination and Therapy

Clincial work-ups at the beginning of the study and during follow-up included history, physical examination, measurement of palpable tumors, photographs of visible lesions, x-ray of chest and skeleton, isotopic skeleton and liver scintigrams, ultrasonic examination of the liver and the abdomen and if necessary computed tomography of the brain, chest, or abdomen; routine blood chemistry included a SMAC 24 program, complete blood counts, and CEA.

All patients were treated according to fixed therapy protocols. Treatment regimes used were predominantly the CMF or the VAC combination and tamoxifen for hormone therapy.

Definition of progression of disease, no change, and partial or complete remission was done according to the recommendations of the UICC (Hayward et al. 1977).

CEA Levels and Prognosis

Serial CEA values up to at least 3 months before death were available for all patients, and for 73 patients (70%) the last CEA determination was performed within 4 weeks before death. Therefore, it was possible to form a group of patients reaching CEA levels $\geqq 10$ ng/ml during disease progression (high-CEA group) and a group with low CEA levels (low-CEA group) who probably never had CEA values >10 ng/ml during metastatic disease. This limit was chosen because previous investigations had shown that CEA levels >10 ng/m did not fluctuate and were reliably disease-related. Both groups were then compared with regard to prognostic factors, survival times, and response to therapy.

CEA Levels and Metastatic Involvement

Some patients with constantly low CEA levels persisting up to their death might have died with low tumor burden involving unfavorable sites, e.g., the CNS, or they might have died of non-disease-related causes. Others might have a subtype of mbc with low capability to secrete CEA. To segregate these possibilities the meatastatic involvement during disease and the causes of death were analyzed. For the latter, hospital files (30% of cases), autopsy records (15%) and interviews with family doctors (70%) were evaluated, using the following definitions: death from disseminated breast cancer without further specification; death from metastatic organ involvement including bone metastases (bone marrow failure, hypercalcemia), abdominal metastases (obstruction by tumor mass, hepatic failure), thoracic involvement (respiratory insufficiency) or CNS involvement (coma); causes that were not directly disease-related were therapy-induced death, infection, and suicide.

The metastatic involvement was classified according to its clinical significance as predominant or not predominant. A few small lesions not impairing organ functions and the condition of the patient or preterminal metastases not influencing the clinical course of disease were defined as not predominant. Then the patients were grouped according to the predominant organ sites using the following definitions:

Bone and liver involvement
Intra-abdominal or intra-abdominal with intrathoracic or intra-abdominal with soft tissue metastases
Bone or bone with thorax or bone with brain or bone with soft tissue
Thorax or thorax with soft tissue or thorax with brain
More than two predominant sites
Others

CEA Assay

The carcinoembryonic antigen in the serum was determined with a solid-phase ELISA, as described in detail elsewhere (Bandlow et al. 1978). The coefficients of interassay variations when testing patient sera with various CEA levels were below 5%. Sera of 300 healthy female subjects varying in age and smoking habits were used as controls. In this control group the mean CEA value and standard deviation were 2.6 ng/ml $\pm$ 0.4.

Statistical Methods

The uncensored survival times were compared by the U-test of Wilcoxon, Mann, and Witney. Response rates were compared using the standard chi-square test.

Results

Follow-up of CEA Levels

The 105 patients with mbc were clinically and biochemically followed for a median period of 25 months (range: 3–54) and a median of 13 CEA determinations (3–54) were performed in each patient before death.

In all but 18 patients, the CEA values rose with progressive disease, reaching the highest level at death. The 18 patients with an unusual pattern of CEA values included 9 who always had CEA values <3 ng/ml with no terminal rise; 3 patients dying in remission of therapy-related organ failure (all 3 belonged to the high-CEA group); 2 patients with isolated cerebral relapse (1 in the low and 1 in the high-CEA group); 3 patients with a preterminal drop in CEA values induced by cytotoxic chemotherapy; and 1 patient with stable disease for whom the cause of death was unknown.

Of the patients evaluated, 39 (37%) had constantly low CEA levels never reaching 10 ng/ml, and 66 (63%) had CEA values $\geqq 10$ ng/ml during follow-up. The two patient groups were compared with reference to prognostic factors, response to chemotherapy, and survival.

CEA Levels and Prognostic Factors

When the two groups were compared for prognostic factors on entry to the study there was no difference between the two groups in median age (59 years), menopausal status, number of involved sites, performance status, or number of previous therapies. The median disease-free interval was significantly ($P=0.01$) shorter in the low-CEA group than in the high-CEA group (11 versus 28 months). More patients with constantly low CEA levels had soft tissue metastases (21% versus 11%), and more patients reaching high CEA levels had osseous metastases (43% versus 24%) on entry to the study. Histological type, lymph node involvement, and receptor status were not different in the two CEA groups. However, these data were not available for all patients. On mastectomy 76% of patients were found to have invasive ductal carcinoma and 6%, other types of breast carcinoma. In 18% of patients no histological type was recorded. Lymph node status was positive in 56% of patients and nega-

Table 1. Distribution of survival times after recurrence in patients with constantly low CEA levels and in patients reaching high CEA levels during disease

		Total	0–12 months	13–24 months	25–36 months	>36 months
All cases	*n*	105	14	33	29	29
	%	100	13	31	28	28
CEA < 10 ng/ml	*n*	39	13	12	9	5
	%	100	33	31	23	13
CEA ≧ 10 ng/ml	*n*	66	1	21	20	24
	%	100	2	32	30	36

Table 2. Metastatic pattern of patients with high (+) and low (−) CEA levels during disease grouped according to survival times[a] after recurrence

Survival time (months)	Liver and bone	Abdomen; abdomen and thorax; abdomen and soft tissue	Bone; bone and thorax; bone and brain; bone and soft tissue	Thorax; thorax and soft tissue; thorax and brain	>2 Predominant sites	Others	Total (*n*)
13–24	6+/0−	3+/2−	5+/3−	0+/4−	4+/2−	2* +/1**− 1**+	33
25–36	8+/0−	2+/1−	6+/4−	1+/3−	2+/1−	1* +/0−	29
>36	5+/0−	3+/1−	12+/2−	2+/2−	2+/0−	0 +/0−	29
Total (*n*)	19	12	32	12	11	5	91

[a] Patients with survival times < 12 months (1+; 13−) are described in the text
* Death during remission
** Isolated cerebral relapse

tive in 21%, and in 23% the lymph node status were unknown at mastectomy. Hormone receptor status were only available for 57% of patients: 33% positive and 24% negative.

CEA Levels and Response to Therapy

When the response rates to chemotherapy in the two groups were compared, the patients with high CEA levels responded slightly better to the first chemotherapy, and distinctly better to the second trial, than the patients with low CEA values (first trial: 33% remission, 32% no change, 35% progression, $n=66$ versus 30%, 17% and 53%, $n=39$; second trial: 14% remission, 28% no change and 58% progression, $n=36$ versus 5%, 5% and 90%, $n=26$). However, these differences were not statistically significant.

CEA Levels and Prognosis

The median survival of the 66 patients reaching CEA levels ≧ 10 ng/ml was 65 months (range: 11–234) after mastectomy and 28 months (11–98) after first recurrence. The 39 patients with constantly low CEA had a median survival of 39 months (4–93) after mastectomy and of 18 months (3–64) after recurrence. The difference was highly significant ($P=0.001$).

As shown in Table 1, the shorter median survival of patients with low CEA levels during disease was due first to a subgroup of patients with very short survival (< 12 months) in the low-CEA group, and secondly to some patients with high CEA levels and very long survival (> 36 months).

CEA Levels and Metastatic Involvement

The patients in the subgroup with very short survival were difficult to allocate to the given categories of predominant metastatic involvement. Therefore they were considered separately. Only one of these patients had high CEA levels. This was a 59-year-old patient with clinically diagnosed soft tissue, bone, and thoracic involvement, who died of mitomycin-induced lung fibrosis (confirmed by autopsy). All the 13 remaining patients with low CEA levels died of disseminated breast cancer; all had at least two, and nine at least three, involved sites at recurrence. Ten had intra-abdominal metastases and four, cerebral involvement during disease. These data suggested the presence of a group of patients with rapidly progressive and widespread breast cancer dying with an evidently large tumor burden but without reaching high CEA levels until death. Five to these patients had no terminal rise of CEA, and eight had a preterminal increase of CEA up to values between 3.1 and 8.5 ng/ml.

When patients with survival times > 12 months were analyzed, two further difference responsible for

the poorer prognosis of patients with low CEA levels during disease were identified. As shown in Table 2, comparatively more patients with low CEA levels had thoracic involvement and short survival, whereas distinctly more patients in the high-CEA group had bone metastases and long suvival. All patients with extensive bone and liver involvement were in the high-CEA group and had survival times comparable to those of the entire group when the patients with very short survival were excluded.

Discussion

CEA blood levels in metastatic breast cancer depend on several factors, such as the ability of tumor cells to secrete CEA, the tumor mass, the metastatic pattern and host factors, which have not yet been precisely defined (Tormey et al. 1977). Therefore the causes of the shorter median survival of patients with constantly low CEA levels were probably complex and heterogeneous. However, analysis of the clinical data revealed two main differences between the low- and the high-CEA group, which could explain the shorter median survival of patients with low CEA levels during disease.

One difference was the higher proportion of patients with lung involvement and poor prognosis and the lower proportion of patients with bone metastases and long survival in the low-CEA group. An obvious explanation would be that patients with lung involvement died with a smaller tumor burden, which caused vital dysfunction when infiltrating the lungs, but was tolerated when infiltrating the bones. However, it has been suggested that tumors secreting large amounts of CEA might preferentially home to bones and liver (Tormey et al. 1977).

The second difference was the presence of a subgroup with very poor prognosis among the patients with low CEA levels. This group included patients with very short survival, widespread metastatic disease, and evidently large tumor mass.

Some of these patients might have rapidly proliferating undifferentiated cancers, which secrete only low amounts of CEA. In vitro studies on colon carcinoma cells showed that the production and secretion of CEA was cell-cycle-dependent. Exponentially growing cells secreted lower amounts of CEA than tumor cells in the stationary and G1 phase (Drewinko and Yang 1980). Furthermore, the CEA content of tumor cells was usually higher, with a more highly differentiated tumor type in colon cancer (Denk et al. 1972).

A similar correlation was found in primary breast cancer at mastectomy (Walker 1980), but was not confirmed by others (Wahren et al. 1978). When the histochemical CEA status of lymph node metastases at mastectomy was correlated with prognosis in patients with breast cancer it was found that patients with CEA-negative lymph node metastases had the poorest prognosis (time to relapse), which was not improved by adjuvant chemotherapy (Smith et al. 1982). Patients with strongly CEA-positive lymph nodes had the best prognosis, followed by patients with weakly positive staining who benefited from adjuvant chemotherapy. However, there was no correlation between CEA status and histological grading in this study. Further investigations, which correlated histological grading, CEA status, and prognosis in more advanced breast cancer have not been published.

In conclusion, the clinical data presented suggest that there might be a biological subgroup of rapidly disseminating breast cancers with diminished CEA secretion. However, this interpretation has to be confirmed by clinicopathological studies, which correlate the clinical data with histological grading and CEA staining in autopsy material from metastatic breast cancer.

References

Bandlow G, Douwes F, Mross K (1978) Ein einfacher Festphasenradioimmuntest zum Nachweis des carcinoembryonalen Antigens. Arztl Labor 24:157–161

Bezwoda W, Derman D, Bothwell T, MacPhil P, Levin J, DeMoor N (1981) Significance of carcinoembryonic antigen, ferritin, and calcitonin in breast cancer. Cancer 48:1623–1628

Denk H, Tappeiner G, Eckerstorfer R, Holzner JH (1972) Carcinoembryonic antigen (CEA) in gastrointestinal and extragastrointestinal tumors and its relationship to tumor cell differentiation. In J Cancer 10:262–272

Drewinko B, Yang LY (1980) Observations on the synthesis of Carcinoembryonic antigen by an established human colonic carcinoma cell line. Oncology 37:336–342

Hayward JL, Carbone PD, Heuson JC, Kumaoka S, Segaloff A, Rubens RD (1977) Assessment of response to therapy in advanced breast cancer. Cancer 39:1289–1295

Rozencweig M, Heuson JC (1975) Breast cancer: prognostic factors and clinical evaluation. In: Staquet MJ (ed) Cancer therapy: prognostic factors and criteria of response. Raven Press New York, p 139

Smith SR, Howell A, Minawa A, Morrison JM (1982) The clinical value of immunohistochemically demonstrable CEA in breast cancer: a possible method of selecting patients for adjuvant chemotherapy. Br J Cancer 46:757–764

Tormey DC, Waalkes TP, Snyder JJ, Simon RM (1977) Biological markers in breast carcinoma. Cancer 39:2397–2404

Tormey DC, Waalkes TP (1978) Clinical correlation between CEA and breast cancer. Cancer 42:1507–1511

Wahren B, Lidbrink E, Wallgren A, Eneroth P, Zajicek I (1978) Carcinoembryonic antigen and other tumor markers in tissue and serum or plasma of patients with primary mammary carcinoma. Cancer 42:1870–1878

Walker RA (1980) Demonstration of carcinoembryonic antigens in human breast carcinomas by the immunoperoxidase technique. J Clin Pathol 33:356–360

Received June 1, 1984/Accepted July 18, 1984