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CLINICAL TRIAL REPORT

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Treatment of disease-negative but mucin-like carcinoma-associated antigen-positive breast cancer patients with tamoxifen: preliminary results of a prospective controlled randomized trial

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Abstract Increasing levels of tumor markers such as carcinoembryonic antigen, mucin-like carcinoma-associated antigen (MCA), CA 15.3, and monoclonal antibody H23 in breast cancer patients following the treatment of the primary disease and adjuvant radiation and chemotherapy reflect subclinical development of metastatic disease. Overt metastatic disease is usually incurable and prolongation of life at this stage is impossible, and the treatment is only palliative. The efficacy of tamoxifen, a least-toxic agent, in the treatment of early and minimal metastatic disease detected only by increasing serum levels of MCA was studied prospectively in a randomized study. Our preliminary, albeit encouraging, results showed that the rate of relapse within a median follow-up period of 11 months was 24.1% in the control arm as compared with 0% in the tamoxifen arm (Fisher's exact test, $P = 0.012$). None of the patients with a relapse had positive progesterone receptors (PR). We may carefully conclude that early treatment may be warranted in young patients with negative PR and continuously increasing serum levels of the marker.

Key words Breast cancer · Tamoxifen · Metastatic disease · Tumor markers · Carcinoembryonic antigen · Mucin-like carcinoma-associated antigen · CA 15.3

Introduction

Contemporary follow-up programs for breast cancer patients are based on periodic routine history and physical examination and a yearly mammography. Routine use of chest X-rays, bone and liver scans, and other ancillary tests may not be justified because the survival remains unaffected [13, 14].

Tumor markers such as carcinoembryonic antigen (CEA), mucin-like carcinoma-associated antigen (MCA) [5, 8, 10, 11], CA 15.3 [1, 2, 5], and monoclonal antibody (mAb) H23 [9, 15] may play an important role in early detection of relapsing disease and in monitoring of the treatment. Modern breast cancer markers such as MCA are characterized by high sensitivity (87.5%) and specificity (76.9%) and by a high positive predictive value (82.3%) [8].

The treatment of either symptomatic or asymptomatic gross metastatic breast cancer is unrewarding in terms of life expectancy. No curative modality has yet been developed, and current treatment does not lead to prolongation of the patient's survival [3, 6]. On the other hand, treatment of a subclinical tumor-load detected only by elevated levels of serum tumor markers *may* prevent or delay the appearance of symptoms. A clear clinical benefit, however, has thus far not been demonstrated.

The role and importance of MCA and other tumor markers in early detection of metastatic breast cancer has been discussed elsewhere [8, 9]. It has not yet been established whether the marker level itself, the slope of the marker curve, or the change in the slope within a certain period is predictive of the metastatic surge. Our data support the use of the increasing slope observed after MCA has crossed its cutoff level of 14 U/ml as a predictive sign [8, 9]. The slope evolution characterizes the development of the disease in each individual patient and represents the tumor biology, provided that the tumor cells secrete MCA. Elevated levels of tumor markers can precede the appearance of overt metastases by more than 40 months [9]. One may assume that early treatment of clinically undetectable disease on the basis of an elevated serum level of a sensitive and reliable tumor marker may improve the treatment results and even prolong the patient's survival. This report presents the preliminary results of a continuing prospective randomized study of the administration of tamoxifen to breast cancer patients exhibiting elevated serum levels of

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breast-cancer-associated markers but no clinical or radiological evidence of disease.

Patients and methods

Patients

A total of 52 women with histologically proven breast carcinoma but without any other concurrent malignancy were accrued to the study within a period of 36 months. The patients' characteristics are presented in Table 1. All the patients were treated for stage I or II invasive carcinoma of the breast. They underwent either a modified radical mastectomy or a lumpectomy and axillary node dissection as well as adjuvant radiotherapy to the breast. Node-positive patients or node-negative patients with a tumor measuring >3 cm in diameter received adjuvant systemic treatment. Postmenopausal estrogen receptor (ER)-negative patients under 65 years of age and all premenopausal women received cyclophosphamide/methotrexate/5-fluorouracil (CMF) chemotherapy. Postmenopausal (ER-negative or -positive) patients over 65 years of age with node-positive disease or with node-negative disease measuring >3 cm in diameter were treated with tamoxifen and were thus excluded from the study.

All the patients were symptom- and disease-free at the beginning of the follow-up period but gradually showed increasing serum levels of MCA in at least two consecutive measurements. No detectable disease was found on systemic workup, i.e., a physical examination, chest X-ray, liver ultrasound examination, and bone scan. Patients were randomly allocated to one of two groups whenever they had at least two consecutive measurements above the cutoff level or a change in the uprising slope of the marker level. One group received 10 mg tamoxifen twice a day indefinitely or until the development of recurrence, and the other group served as a control without any treatment. Patients in relapse were treated according to the type and site of their disease.

Table 1 Patients' characteristics (*Ax. diss.* Axillary node dissection, *ER* estrogen receptor, *PR* progesterone receptor)

	Control arm	Tamoxifen arm
Number of patients	29	23
Age at diagnosis:		
Range	34–77 years	39–70 years
Median/mean	50/52.7 years	52/54.1 years
Menstrual status:		
Pre-/postmenopausal	17/12	8/15
Histology:		
Infiltrating ductal	21	20
Infiltrating ductal and lobular	1	1
Infiltrating lobular	4	2
Medullary carcinoma	1	–
Mucoid carcinoma	1	–
Tubular carcinoma	1	–
Stage (all are MO):		
TxNO	–	2
T1NO	16	5
T1N1	4	4
T1mNO	2	2
T1mN1	1	–
T2NO	3	6
T2N1	1	3
T2mNO	1	–
T2mNx	1	–
T3NO	–	1
Treatment of primary disease:		
Lumpectomy, ax. diss.	15	10
Modified radical mastectomy	14	13
Receptor status:		
ER-positive	8	11
ER-negative	12	9
ER unknown	9	3
PR-positive	4	6
PR-negative	16	13
PR unknown	9	4

Protocol

Baseline assessments, including physical examinations, chest X-rays, liver ultrasound examinations, radioisotope bone scans, computerized tomography (CT) of the chest and abdomen, complete blood counts (CBC), biochemical panels including liver-function tests, and measurements of MCA serum levels, were obtained for each patient. Follow-up included periodic (every 3–6 months) physical examinations, CBC, biochemical panels, measurements of MCA serum levels, and yearly mammography. Ancillary tests were carried out according to the patients' complaints. Patients were to be withdrawn from the protocol if clinically overt metastatic disease had developed.

Measurement of tumor markers

An MCA level of ≥14 U/ml was considered pathological, whereas lower levels were considered normal [4, 10, 12]. Blood samples were drawn and kept at 4 °C for 4–6 h until separated. Sera were kept at –20 °C until assayed in duplicate for tumor marker levels, and the mean value was calculated. Serum MCA measurement was carried out using an enzyme immunoassay (EIA) kit (Hoffmann La-Roche, Switzerland).

Calculations and statistical analysis

The lead time was calculated from the first measurement of a pathologically elevated serum level of MCA, i.e., when the marker had crossed the cutoff level, until the development of overt metastatic disease. The event-free interval (EFI) was defined as the period ranging from the surgical treatment of the primary lesion to the documentation of overt metastatic disease. The term *EFI* was preferred over *disease-free interval (DFI)* because, in our opinion, increasing serum levels of tumor markers reflect the development of disease.

The end points of our study comprise the time to the development of overt metastatic disease, the rate of local recurrence and distant metastases, and the overall survival of the patients in both arms. Statistical analysis included descriptive statistics and Fisher's exact test. A P-value of <0.05 was considered significant.

Results

The overall follow-up period as determined from the day of surgery for the primary tumor ranged from 51 to 484 weeks. Within a median follow-up period of 48 (range, 13–148) weeks after randomization, none of the patients randomized for tamoxifen has relapsed, whereas 7 patients in the control arm (7/29, 24.1%) have developed overt recurrent loco-regional or metastatic disease (Table 2). This difference in relapse rate was statistically significant (P = 0.012). The EFI of the seven patients in the control arm who relapsed ranged from 39 to 462 weeks, whereas their lead time ranged from 13 to 290 weeks. One patient developed a T_1N_1 contralateral breast-infiltrating ductal carcinoma, two patients (28.6%) experienced local relapses, and one patient (14.3%) developed ipsilateral axillary lymph node metastases. Three patients (42.8%) had distant metastases in the

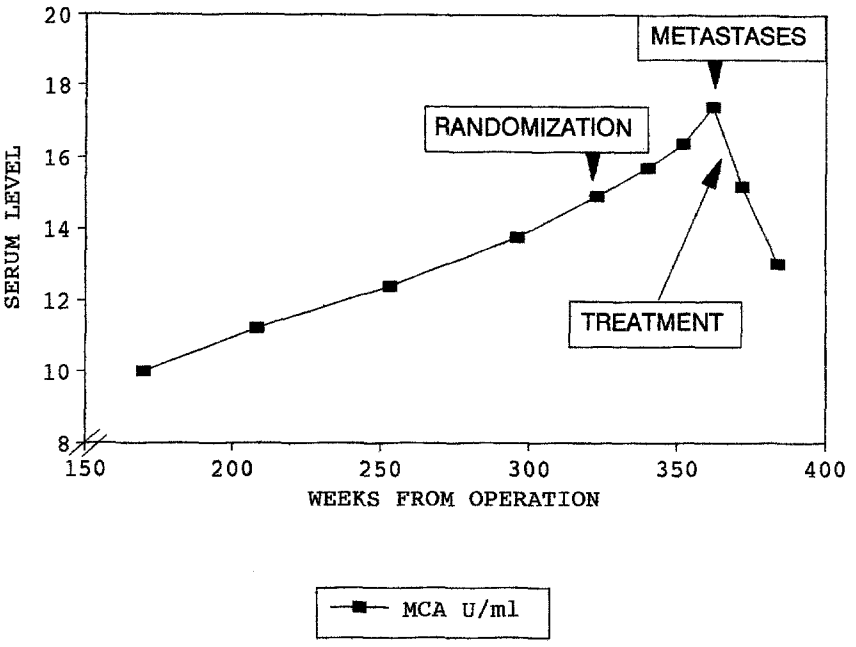

Fig. 1 A case from the control arm. T.T., a-64-year-old postmenopausal patient with aT1N1M0 (1 positive node out of 7) ER-positive, PR-negative, infiltrating ductal carcinoma, underwent (in another center) a modified radical mastectomy followed by adjuvant chemotherapy. Note the moderately uprising slope of the serum level of MCA until the appearance of overt metastatic disease. The subsequent rapid decline is due to treatment of the overt metastatic disease in the lung and bone with tamoxifen

lungs, the lungs and bones (Fig. 1), and the bones and lymph nodes, respectively. Another patient had multiple nodal and diffuse bone involvement. Lymph node and bone marrow biopsies undertaken in this patient surprisingly revealed non-Hodgkin's lymphoma. A thorough workup could not detect metastases of breast cancer in any site, leaving the mystery of her increasing levels of MCA unresolved. This case was not included in the statistical analysis. Since there was no relapse in the tamoxifen arm, neither the EFI nor the lead time could be calculated. The serum levels of MCA measured in patients belonging to the control arm at the time of the first documentation of overt metastatic disease ranged from 15.17 to 19.76 U/ml (mean, 16.88 U/ml). The survival rate of patients in both arms was 100% at the date of this writing.

The characteristics of the patients with recurrent disease (from the control arm) were analyzed. Their age (range, mean, and median), menstrual status, histological type of primary tumor, ER status, disease stage and treatment of the primary disease were similar to those of the other patients in the control arm. However, none of the patients experiencing a relapse was PR-positive. A negative PR status was significantly ($P < 0.001$) more common in those who experienced a relapse.

Measurement of the serum level of MCA was the only way to monitor the efficacy of tamoxifen in patients with no evidence of disease. The influence of tamoxifen on the pretreatment increase in serum levels of MCA was characterized either by a downward slope of the curve followed by a reincrease in the serum level (Fig. 2), by plateau formation, or by a lack of change in the baseline trend of the marker.

Table 2 Preliminary results (*NED* No evidence of disease)

	Follow-up	Tamoxifen
Accrued patients (*n*)	29	23
Median follow-up (months)	11	11

	Disease status		Disease status		*P* value
	Relapse	ned	Relapse	ned	
Cases (*n*)	7[a]	21	0	23	0.012[c]
Follow-up period (months)	6–35		3–34		
Lead time (months)[b]	3–12		–		

[a] Relapses included 1 case of contralateral T_1N_1 infiltrating ductal carcinoma, 2 cases of local relapse, 1 case of ipsilateral axillary lymph-node metastasis, and 3 cases of distant metastasis. Another patient had signs of metastatic disease, but bone marrow biopsy surprisingly showed non-Hodgkin's lymphoma

[b] The lead time represents the period ranging from the first measurement of increased marker levels until the appearance of a relapse

[c] According ot Fisher's exact test

Discussion

Our data showed that the nontreated disease-negative MCA-positive breast cancer patients experienced a significantly higher rate of relapse (24.1%) than did the tamoxifen-treated subjects (0%; $P = 0.012$). The majority of recurrences were distant (57%), but local recurrences (two cases) and regional lymph node metastases (one case) were also observed. One case of contralateral breast primary invasive carcinoma was also diagnosed. The case of non-Hodgkin's malignant lymphoma detected as a result of elevation of MCA levels cannot be explained at this time, and further follow-up is required. However, it could represent an independent second malignancy synchronous with a yet-occult recurrent breast cancer. We do not have

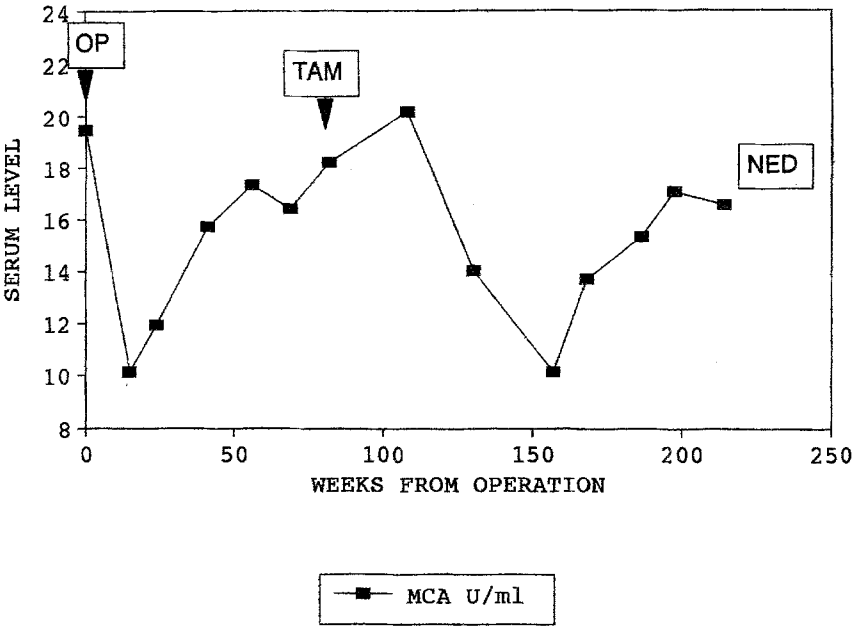

Fig. 2 A case from the tamoxifen arm. K.B., a-49-year-old premenopausal patient with a T1N1M0 ER-positive, PR-negative, infiltrating ductal carcinoma, underwent a lumpectomy and axillary node dissection followed by radiation therapy to the breast and adjuvant chemotherapy. Note the postoperative decline and subsequent increase in the MCA level. The administration of tamoxifen was delayed until the next measurement due to the unexpected small decline in the MCA level. Tamoxifen treatment caused a rapid decrease that lasted for 1 year and was followed by an increase. The patient currently shows no evidence of disease. (*OP* Operation, *TAM* tamoxifen treatment, *NED* no evidence of disease)

data regarding increased MCA levels in lymphomas. Our preliminary results point out that the early treatment of marker-positive but clinically undetectable recurrent breast cancer may influence the disease-free survival. To the best of our knowledge, the only other study reported in the literature on this topic has been published in the form of an abstract [7]. The preliminary results showed that the treatment of disease-negative but marker-positive breast cancer patients with medroxyprogesterone acetate (MPA) reduced the risk for overt metastatic disease.

Our data suggest that even in a small series of patients, early treatment may be warranted in young patients who are PR-negative and exhibit continuously increasing serum levels of the marker. Although the study has not yet reached maturity and the trial is continuing, the preliminary results are very encouraging. Further studies in a larger number of patients are, of course, necessary to determine the influence of treatment of early metastatic breast cancer on the outcome of this disease.

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