The Value of Serial Plasma Levels of Carcinoembryonic Antigen and Gross Cyst Disease Fluid Protein in Patients with Breast Carcinoma and Osseous Metastases

DARROW E. HAAGENSEN, JR., M.D., PHD.,* WILLIAM F. BARRY, JR., M.D.,† THOMAS A. MCCOOK, M.D.,† JAN GIANNOLA, R.N.,* SHERRE AMMIRATA, R.N.,* SAMUEL A. WELLS, JR., M.D.*

From the Departments of Surgery and Radiology, Duke University Medical Center, Durham, North Carolina

Serial plasma levels of the glycoprotein tumor markers carcinoembryonic antigen (CEA) and gross cyst disease fluid protein (GCDFP) were evaluated in 83 patients undergoing treatment for predominant osseous metastases from breast carcinoma. Abnormal plasma levels of CEA (>10 ng/ml) and/or GCDFP (>150 ng/ml) were observed in 53 (63.8%) subjects. Fifty-six courses of hormonal and chemical therapy were evaluated. Clinical response to therapy correlated positively with alterations in serial plasma levels of CEA and/or GCDFP. Increasing plasma levels of tumor markers were associated with clinical disease progression whereas decreasing plasma levels were associated with and generally preceded clinical disease remission. Of patients with metastatic carcinoma of the breast, responses to therapy are most difficult to evaluate in those with bone metastases. Serial determinations of plasma levels of CEA and/or GCDFP provide an objective indication of disease progression and regression and appear to be useful with skeletal x-rays and bone scans in evaluating patients with carcinoma of the breast.

IN PATIENTS WITH breast carcinoma metastatic to soft tissue, parenchymal lung, liver or brain, therapeutic response is relatively easily determined by documenting changes in tumor deposit size. By contrast, osseous metastases are more difficult to assess. Abnormal tracer accumulation on bone scan is not specific for malignant disease and even if metastatic foci are evident by conventional skeletal x-rays, response to treatment is often apparent only after long periods of observation. In such patients whose metastatic disease is difficult to evaluate, it would be useful to have other objective methods of defining disease progression or regression soon after the initiation of hormonal or chemical therapy.

Several tumor markers have been reported by various investigators[1-4] to be present in the plasma of patients with metastatic carcinoma of the breast. Carcinoembryonic antigen (CEA) has been the most widely used marker, however, elevated plasma CEA levels have been reported not only with malignancies of tissue other than breast, but also with various infectious and metabolic diseases.[5-8]

In 1977 a new plasma marker for breast carcinoma was described.[9] This substance is a glycoprotein which has been purified from human breast gross cyst disease fluid.[10] The protein has a monomer molecular size of 15,000 daltons and has been termed gross cyst disease fluid protein-15 (GCDFP-15). A radioimmunoassay has been developed for this protein and a large number of subjects evaluated.[11,12] Normal women were found to have plasma levels below 100 ng/ml (range: 7–81 ng/ml); mean: 31 ng/ml; however, 40–50% of patients with metastatic carcinoma of the breast had elevated (>150 ng/ml) plasma levels of this marker. Comparative studies evaluating plasma levels of CEA and GCDFP-15 as markers for human breast carcinoma have been reported.[11] Approximately 27% of patients with metastatic carcinoma of the breast and soft tissue metastases have elevated plasma CEA and GCDFP-15 levels, whereas 54% of those with visceral metastases and 61% of those with osseous metastases have elevated levels. Because a relatively high proportion of patients with skeletal metastases from breast carcinoma develop elevated plasma levels of CEA and GCDFP and because disease progression and regression are difficult to evaluate, we sought to compare changes in plasma marker levels during the administration of hormonal or chemical therapy with the clinical and skeletal x-ray evaluation of these patients.

Presented at the Annual Meeting of the Southern Surgical Association, December 3–5, 1979, Hot Springs, Virginia.

* Department of Surgery.

† Department of Radiology.

Reprint requests: Darrow E. Haagensen, Jr., M.D., Ph.D., Box 3236, Duke University Medical Center, Durham, North Carolina 27710.

Submitted for publication: December 7, 1979.

0003-4932/80/0500/0599 $00.75

TABLE 1. *Criteria of X-ray Evaluation*

Progression
The change from a normal bone pattern to a lytic bone pattern in any given area.
The increase in size of a lytic bone pattern in any area.
The increase in number of lytic defects in any given area.
The change from a blastic to a lytic bone pattern.
Regression
The change from a normal bone pattern to a blastic bone pattern in any given area. This is felt to represent an area of active tumor cells which is not large enough to be seen on the initial radiograph which responds to treatment and develops a blastic bone pattern.
Increased size of a blastic area within bone.
Increasing number of blastic areas within bone.
The development of a sharply demarcated margin at the edge of the lytic lesion. Most often this occurs with a thin blastic or sclerotic rim. This finding alone is a borderline change. However, it seems to be a real finding and most often the thin rim will become thicker on the next study. This type of change has also been seen in patients who are also converting lytic lesions to blastic lesions in other areas. The increased resolution of the edge of a lytic lesion has been seen most often in the skull.
Bony regeneration of a previous lytic area. When relatively frequent followup studies are available, 1 to 2 month intervals, this type of lesion tends to go on to produce a blastic bone pattern.
The presence of a "mixed blastic and lytic" pattern in a bony area probably implies tumor coming under control of hormone manipulation. However, this can only be a valid conclusion when previous studies are available and show only a dominant lytic pattern.

One other type of pattern has also become apparent. In a patient who had developed blastic lesions, these areas begin to regress until the bone has a normal trabecular pattern. There have been three such patients. Two of the three have subsequently developed lytic areas while one patient has had a normal bone pattern. The change from blastic to normal must at present be considered stable or indefinite.

Materials and Methods

Eighty-four patients with breast carcinoma metastatic predominantly to bone were evaluated at the Duke University Medical Center Surgical Breast Clinic. Fifty-three (61%) were found to have elevated plasma levels of either CEA (>10 ng/ml) or GCDFP (>150 ng/ml) or both markers. After excluding patients who received therapy for less than one month or those who did not have bone x-rays performed during the four months after initiation of therapy, 30 patients were available for study. Nineteen regimens of chemical therapy, 34 regimens of hormonal therapy, and three regimens of mixed chemical and hormonal therapy were evaluated. Patients were seen at weekly or bi-weekly intervals during the early stages of treatment and those who demonstrated clinical disease regression or stabilization were generally followed at monthly intervals. Response to therapy was defined as either regression, stabilization, or progression. In patients evaluated clinically with no evidence of extraskeletal metastatic involvement, response was primarily based on subjective changes in bone pain and performance status. A time frame of four months from initiation of therapy was used to determine response status. Decisions to change therapy were based on clinical and radiographic evidence of disease and not on increases or decreases in plasma marker levels.

Skeletal x-ray evaluation was performed by two of the authors (WFB and TAM). All x-rays on a given patient were reviewed by one radiologist at a single sitting without knowledge of either the patient's clinical status or plasma marker status. Criteria for x-ray interpretation are presented in Table 1. The x-ray findings were also interpreted as regression, stability or progression. For clinical purposes, the x-rays were actually read at the time they were obtained, however, the second reading by a single radiologist viewing the serial x-rays over a patient's entire treatment course was done to more clearly define the radiologic evidence of response.

The CEA and GCDFP-15 plasma marker determinations were performed at each clinic visit for all patients. The CEA plasma levels were measured with the CEA-Roche radioimmunoassay.[12] The GCDFP-15 plasma levels were also measured by radioimmunoassay.[10-12] Blood samples (K3EDTA) were obtained prior to the patient's physical exam and specific therapy. The plasma was separated within three hours and frozen at −70 C until analysis. A significant increase in either the plasma level of CEA or GCDFP-15 was defined arbitrarily as a doubling of the value obtained prior to initiation of therapy. Similarly, a significant decrease in plasma marker level was defined as a halving of the pretreatment value. Numericaly this meant that a significant increase represented a 100% increase over the pretreatment value, whereas a significant decrease represented a 50% decrease below the pretreatment

TABLE 2. *Comparison of Clinical Evaluation of Disease Status with Serial Skeletal X-ray and Plasma Marker Profile Evaluation*

Clinical Evaluation	Skeletal X-ray Evaluation		Plasma Marker Profile Evaluation	
Regression (17)	R 10 S 3 P 4	76%	R 10 S 5 P 2	88%
Stable (25)	R 9 S 6 P 10	60%	R 6 S 7 P 12	52%
Progression (14)	R 0 S 5 P 9	64%	R 1 S 2 P 11	79%
56	—		—	

R = Regression.
S = Stable.
P = Progression.

value. The time during which plasma levels of CEA or GCDFP were evaluated was four months from initiation of therapy. The plasma marker level alteration within this time frame had to be a serial trend for the designation of disease progression or regression. Minimal alteration was interpreted as marker stability.

Results

Clinical Regression

There were 17 courses of chemical or hormonal therapy which induced clinical disease regression (Table 2). Eight of the courses were with chemical therapy and nine with hormonal therapy. The interpretation of changes in skeletal x-rays and plasma levels of tumor markers were compared with clinical evidence of disease remission. Patients who had x-ray or plasma marker evidence of disease regression or stabilization were characterized as being compatible with clinical regression. X-ray or marker evidence of disease progression, was obviously interpreted as being incompatible with clinical regression. Of the 17 courses of therapy, 13 (76%) had associated x-ray findings of disease regression or stabilization. Fifteen (88%) of the 17 courses of therapy were associated with plasma marker evidence of disease regression or stabilization.

Clinically Stable Disease

Twenty-five courses of chemical or hormonal therapy were associated with clinical evidence of disease stability (Table 2). Only a small proportion of therapeutic courses demonstrated x-ray (6; 24%) or plasma marker (7; 28%) evidence of disease stabilization. Ten (40%) therapeutic courses were associated with x-ray evidence and 12 (48%) with plasma marker evidence of disease progression.

Clinical Progression

There were 14 courses of chemical (2) and hormonal (12) therapy associated with clinical evidence of disease progression. Eleven (79%) of these 14 courses of therapy were associated with plasma marker evidence of progression while nine (64%) had skeletal x-ray evidence of disease progression. Skeletal x-rays were interpreted as stable in five (36%) patients. In two patients plasma markers were stable and in one, the marker levels significantly decreased. This single patient also had a stable x-ray evaluation and clinical progression was based solely on an increase in back pain.

TABLE 3. *Skeletal X-ray versus Clinical Evaluation of Disease Status*

Skeletal X-ray Evaluation		Clinical Evaluation	
Regression	(19)	R 10 S 9 P 0	100%
Stable	(14)	R 3 S 6 P 5	64%
Progression	(23)	R 4 S 10 P 9	39%
	56		

TABLE 4. *Plasma Marker Profile versus Clinical Evaluation of Disease Status*

Plasma Marker Profile Evaluation		Clinical Evaluation	
Regression	(17)	R 10 S 6 P 1	94%
Stable	(14)	R 5 S 7 P 2	86%
Progression	(25)	R 2 S 12 P 11	44%
	56		

X-ray and Plasma Markers as Primary Response Criteria

When skeletal x-rays were used as the primary criterion of patient response and compared to the clinical status (Table 3), it became apparent that a very favorable correlation (100%) existed between x-ray evidence of regression and clinical evidence of regression or stabilization. In contrast, however, of the 23 therapy courses defined as progression by x-ray, only nine (39%) were thought to be associated with disease progression clinically. In ten (42%) of the 23 therapy courses, the patients were considered clinically stable when x-ray evidence of disease progression was present. Of the 14 therapy courses where x-rays demonstrated stable disease, five (36%) were considered as clinical progression.

When plasma marker level profiles were used as the primary criteria of patient response and compared to clinical evaluation (Table 4) similar results to x-ray evaluation were obtained. For the 17 therapy courses with marker profiles indicating regression, 16 (94%) were thought to demonstrate disease regression or stabilization clinically. A similar favorable correlation existed for the 14 therapy courses with stable marker profiles, where 12 (86%) were considered to have clinical evidence of stabilization. In contrast, of the 25 therapeutic courses where marker levels indicated

TABLE 5. *Time of Definitive Change*

Category of Stratification	Plasma Marker Evaluation	Skeletal X-ray Evaluation
Regression	1.32 mo.	2.7 mo.
Progression	2.0 mo.	2.1 mo.

disease progression, only 11 (44%) had clinical evidence of disease progression.

Time of Definitive Change in Skeletal X-rays or Plasma Markers

The time from initiation of hormonal or chemical therapy to the point in time at which a significant change in plasma marker levels or skeletal x-rays was evident was evaluated. Considering those courses of therapy which were associated with disease regression, decreases in plasma markers were detected in an average of 1.32 months, whereas evidence of regression by skeletal x-rays was not demonstrated until 2.7 months. Of the course of therapy associated with disease progression, changes in plasma marker levels were demonstrated in an average time of two months and skeletal x-rays in an average time of 2.1 months (Table 5).

Discussion

The successful management of patients with metastatic carcinoma of the breast is in part dependent on the capability of detecting disease progression and regression. In patients with bone metastases, therapeutic response is most difficult to evaluate. Generally, healing of lytic metastases is easier to assess than healing of blastic lesions. Bone scans are especially difficult to evaluate during the course of therapy since an increase in the size of a given lesion may indicate bone healing rather than destruction. The accurate documentation of disease status is important since progressing skeletal metastases may result in fracture or hypercalcemia. The availability of "tumor markers" which would accurately reflect the success or failure of therapy for metastatic disease would be of significant use to clinicians.

In the present study an attempt was made to determine the alteration in plasma levels of two markers, CEA and GCDFP-15 and to correlate these markers with the clinical and x-ray evidence of response to therapy. Fifty-six therapeutic courses were evaluated in patients with osseous metastases and elevated plasma levels of one or both markers. It was demonstrated that clinical evidence of disease progression or regression was as accurately or better defined by changes in plasma levels of tumor markers as by changes in skeletal x-rays. Decreases in plasma marker levels indicative of disease regression occurred on an average of 1.3 months after initiation of therapy, whereas skeletal x-ray changes were not usually evident until 2.7 months after therapy. Increases in plasma marker levels and progression on skeletal x-rays appeared similarly at two months after the initiation of therapy, however, changes occurred prior to clinical evidence of disease progression. In patients with metastases where interpretation of skeletal x-rays is difficult or nonconclusive, the use of plasma marker levels is of benefit in the clinical evaluation. The measurement of CEA and GCDFP in plasma seems to offer an objective criterion in addition to skeletal x-rays which may be useful in determining therapeutic response in patients with osseous metastases from carcinoma of the breast.

References

1. Chu T, Nemoto T. Evaluation of CEA in human mammary carcinoma. J Natl Cancer Inst 1973; 51:1119–1122.
2. Hendrick JD, Franchimont P. Radioimmunoassay of casein in the serum of normal subjects and of patients with various malignancies. Eur J Cancer 1974; 10:725–730.
3. Kleinberg DL. Human lactalbumin: measurement in serum and in breast cancer organ cultures by RIA. Science 1975; 190:276–278.
4. Herberman RB. Biological markers in breast cancer. *In* McGuire WL (ed.) Breast Cancer 2, Advances in Research and Treatment, New York, Plenum Medical Book Company, 1979. Pp: 205–258.
5. Logerfo P, Krupey J, Hansen HJ. Demonstration of an antigen common to several varieties of neoplasia. N Engl J Med 285:138–141.
6. Steward DM, Nixon D, Zamcheck N, Aisenberg A. Carcinoembryonic antigen in breast carcinoma patients: Serial levels and disease progression. Cancer 1974; 33:1246–1252.
7. Haagensen DE, Jr., Kister SJ, Vandevoorde JP, et al. Evaluation of carcinoembryonic antigen as a plasma monitor for human breast cancer. Cancer 1978; 42:1512–1519.
8. Hansen HJ, Snyder JJ, Miller E, et al. Carcinoembryonic antigen (CEA) assay, a laboratory adjunct in the diagnosis and management of cancer. J Pathol 1974; 5:139–147.
9. Haagensen DE, Jr., Mazoujian G, Holder WD, Jr., et al. Evaluation of a breast cyst fluid protein detectable in the plasma of breast carcinoma patients. Ann Surg 1977; 185:279–285.
10. Haagensen DE, Jr., Mazoujian G, Dilley WG, et al. Breast gross cystic disease fluid analysis. 1. Isolation and radioimmunoassay for a major component protein. J Natl. Cancer Inst 1979; 62:239–247.
11. Haagensen DE, Jr., Kister SJ, Panick J. et al. Comparative evaluation of carcinoembryonic antigen and gross cystic disease fluid protein as plasma markers for human breast carcinoma. Cancer 1978; 42:1646–1652.
12. Haagensen DE, Jr., Wells SA, Jr. Plasma human breast gross cystic disease fluid assay. *In* Herberman RB (ed.) Compendium of Assays for Immunodiagnosis of Human Cancer, Elsevier/North Holland, New York, 1979. Pp. 397–406.