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Use of Serial Carcinoembryonic Antigen Assays in Detecting Relapses in Breast Cancer Involving High Risk of Metastasis

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Abstract—*Serial CEA assays on serum using the direct radioimmunoassay method (Marcoule, France) were performed on* 76 *breast cancer patients with node involvement or rapid local development of tumors who were undergoing chemotherapy. The patients were followed up for a mean period of* 28 months, *and assays were repeated every* 2.5 months *on average. Out of* 521 *assays performed on* 49 *patients who remained in complete remission, there were* 37 *instances of significant, but transitory, rise in CEA level which, in* 8 *cases, could be attributed to intercurrent benign inflammation. In* 15 *out of* 27 *patients who had relapses, there was a significant and persistent rise in CEA level which, in* 11 *cases, preceded clinical signs by* 6 months *on average. In the* 12 *other cases, CEA level remained constant and normal despite relapse.*

INTRODUCTION

IN RECENT years, chemotherapy and hormonotherapy have made it possible to improve prognosis of breast cancers involving high risk of metastasis, whether these are due to node involvement, in which case adjuvant treatment is started in the absence of any apparent signs of disease, or to rapid local development of tumors [1]. In case of relapse, the effectiveness of these methods of treatment is greater if diagnosis is made as early as possible. It is thus important for the clinician to have at his disposal a sensitive tumoral marker to detect possible relapses, not by clinical means which are often too late, but very early when the effectiveness of therapy is potentially greatest. Among the many possible tumoral markers [2], carcinoembryonic antigen (CEA) has already demonstrated its value in diagnosing spread of breast cancers [3, 4]. The purpose of this study was to assess the role of CEA serial assays in detecting relapses in high risk breast cancer patients.

MATERIALS AND METHODS

The 76 patients studied all had node involvement and/or clinical signs of rapid local development defined by clinical inflammatory signs or at least doubling of tumor volume in less than 6 months. They were usually undergoing chemotherapy after surgery and/or irradiation and were followed up from 9 to 46 months, with a mean period of 28 months.

Physical techniques used to detect metastases were chest X-rays, liver and bone scans, liver ultrasonography and brain computerized tomography. CEA assays were performed every 2.5 months on average.

The method employed was direct radioimmunoassay using the kit supplied by CIS (Marcoule, France). The measurement was performed on 50 μl of serum sample. The antigen used for labelling was a purified human CEA extracted from a liver metastasis of colon cancer. The antiserum raised in rabbits had been absorbed with NCA (non-specific cross-reacting antigen) to avoid interference with this antigen during the assay. The standard curve was obtained with the addition of a normal human plasma pool to assure an equivalent milieu for standards and unknowns. The main steps of the assay were preincubation for 20–24 hr at 20–25°C followed by incubation for 20–24 hr with the tracer and incubation for 1 hr at 20–25°C with an immunosorbent consisting of a second antibody fixed on microcrystalline cellulose. The sensitivity of the assay defined as the lowest detectable CEA level measured with an acceptable precision was 2.5 ± 0.5 ng/ml.

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The upper limit of normal values, as determined from a reference group of 65 non-smokers having no benign affections likely to increase CEA concentration, was set at 10 ng/ml. It has been shown that assay specificity is limited by increased concentrations, between 10 and 40 ng/ml, in cases of tobacco addiction and benign inflammations, thus making interpretation of the results difficult in this range of values. But, as our study involved long-term survey of patients, it was considered more important to determine first of all if a variation in CEA level, relative to previous values, was significant or not, rather than to refer to an absolute level. For this purpose, we consulted a precision graph (Fig. 1) on which the outer curves represent ± 2 standard deviation limits of interassay measurements. Moreover, as indicated hereafter, a significant but isolated rise in level did not necessarily mean a relapse. A significant rise in CEA value was considered as persistent if it was confirmed by two or three successive assays at 2-week intervals. In order to improve assay precision, sera were stored and assays were then performed on successive samples at the same time, so as to conform to intra-assay reproducibility conditions.

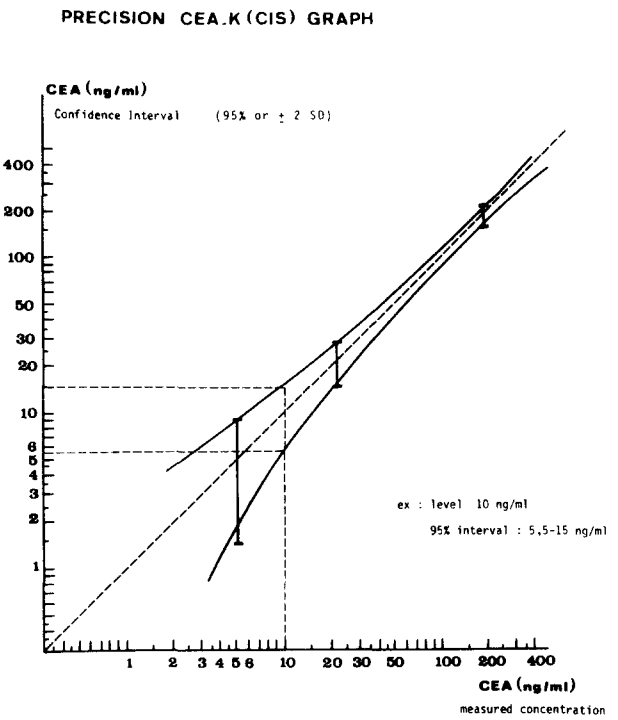

Fig. 1. Precision graph established from inter-assay reproducibility measurements. For example, if the level for an assay is 10 ng/ml, *the next level will be considered as significantly increased if it is above* 15 ng/ml.

RESULTS

Out of the 76 patients in the study, 49 remained in complete remission. For the 521 CEA assays performed on these patients (Fig. 2), the greater majority of values remained under the upper normal limit of 10 ng/ml, although a significant, but very transitory, rise was noted in 37 instances (7%). These increased levels, always under 40 ng/ml, were, in 8 instances, attributable to

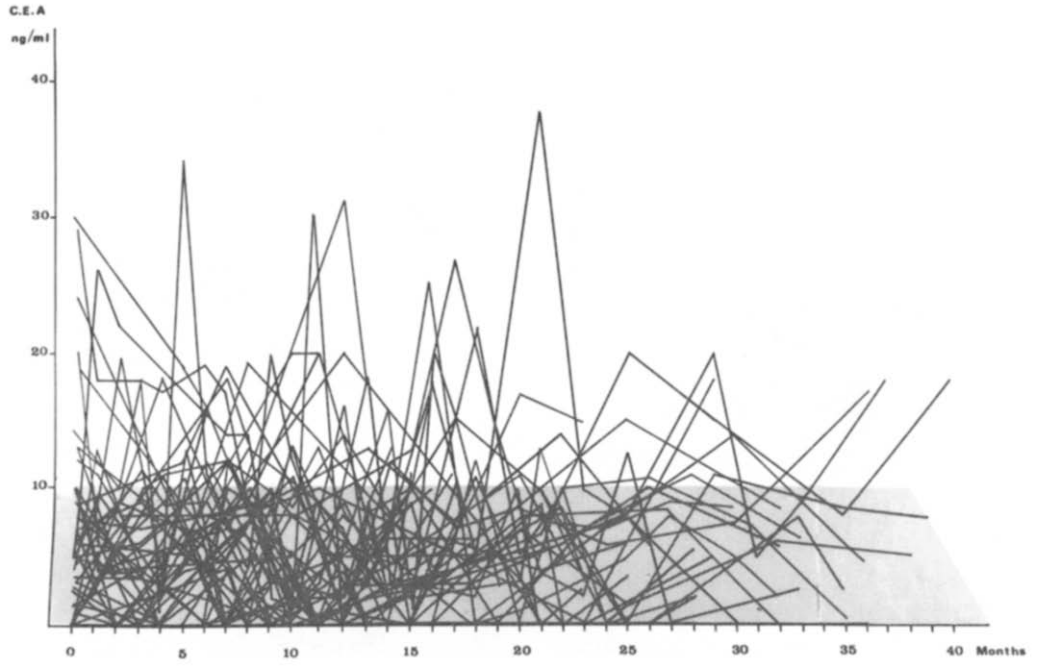

Fig. 2. Kinetics of CEA concentration in patients remaining in complete remission. Shaded area represents the normal values.

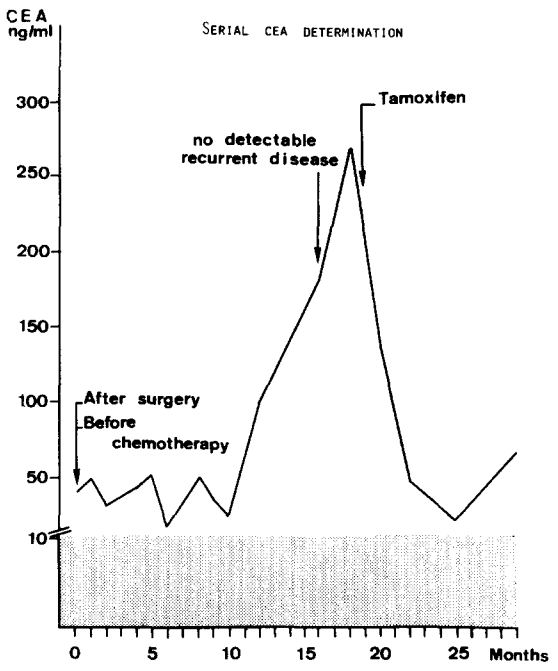

Fig. 3. Kinetics of CEA concentration in a patient with high levels but no apparent signs of clinical or paraclinical relapse.

intercurrent benign inflammation, but no clear explanation could be given for the other 29; in particular, the subjects gave no indication of smoking habits during questioning.

One case (not included in Fig. 2) deserves special mention (Fig. 3). This patient, who had 16 assays over a period of 28 months, with high or very high levels but no apparent signs of clinical or paraclinical relapse, still remains in apparent complete remission. It is worth noting that the decrease in her CEA level was associated with tamoxifen prescription along with polychemotherapy.

The 27 other patients in the study experienced relapse. In 15 cases (56%), relapse was associated with a significant and persistent rise in CEA level, usually above 40 ng/ml (Fig. 4). It should be noted that the initial rise was generally discrete and had to be confirmed before being interpreted as a sign of relapse. Moreover, in 11 of these cases the rise preceded clinical or paraclinical signs of relapse by 1–15 months, with a mean period of 6 months. The sites associated with these 15 relapses were liver and/or bone (9 including 4 widespread), nodes (3) and pleura (3). There was no apparent correlation between changes in CEA level in the serum and those of such inflammatory proteins as haptoglobin (Fig. 5).

Simultaneous and serial assays of CEA and alkaline phosphatase were performed on 8 patients who had relapse affecting only the bones. A rise in CEA was noted in 5 cases 3–9 months before the appearance of clinical signs, whereas the alkaline phosphatase level increased in only 2 cases.

Although 15 relapses out of 27 were correlated with a significant rise in CEA, the 12 others remained below or close to the upper normal values of 10 ng/ml (Fig. 6). The sites of these relapses were local recurrence (3), lung and/or pleura (5), widespread (3) and brain (1).

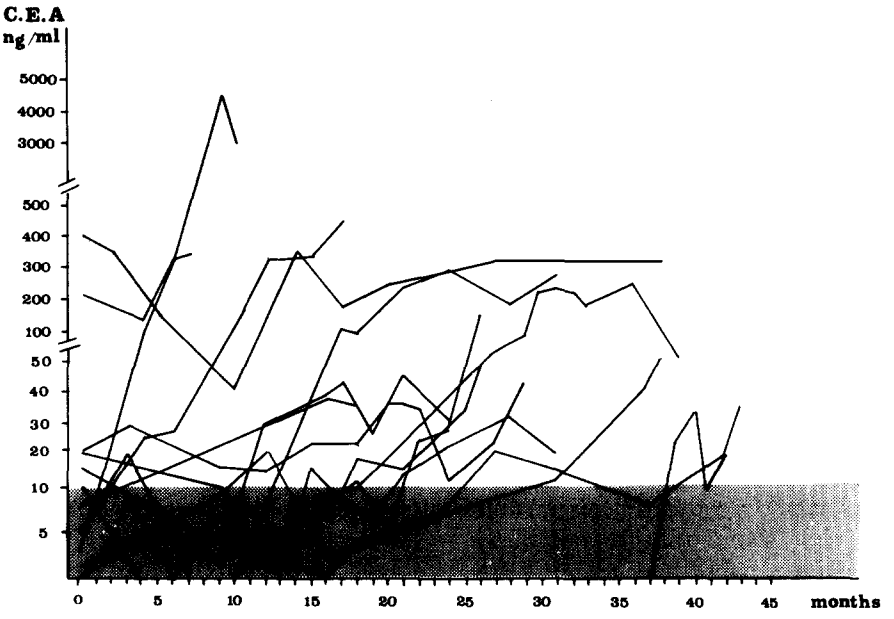

Fig. 4. Kinetics of CEA concentration in 15 patients with relapse associated with a rise in CEA level.

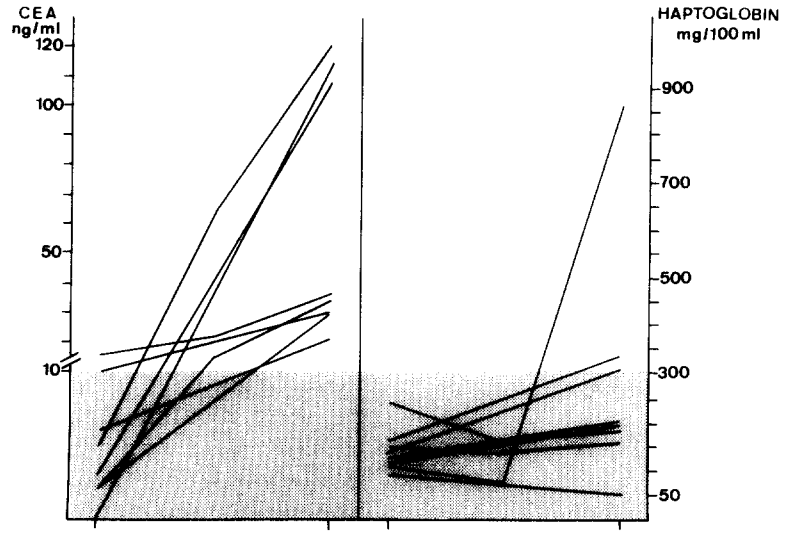

Fig. 5. Simultaneous variation of CEA and haptoglobin in 8 patients with relapse associated with a rise in CEA level: first rise in CEA level (left) and change in haptoglobin level for the same period (right).

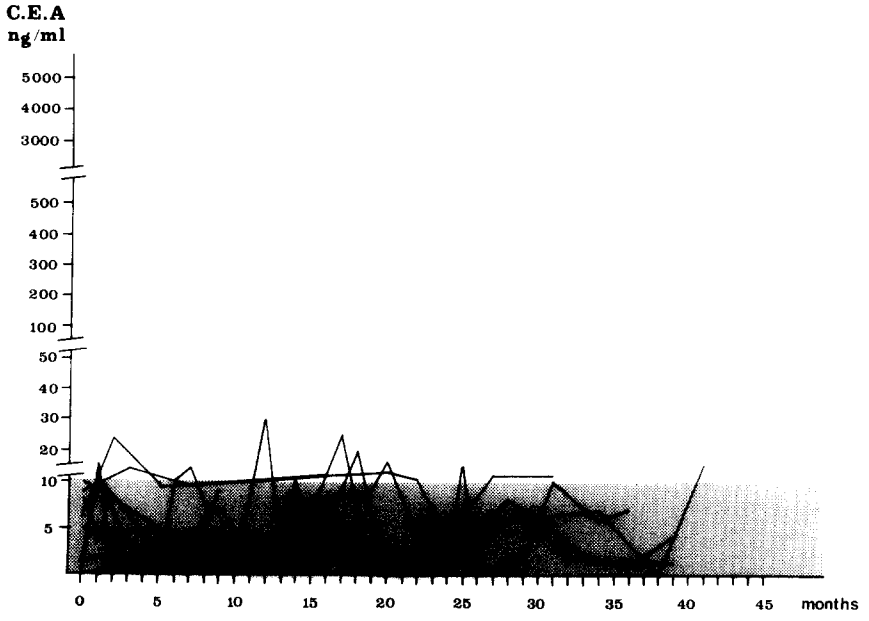

Fig. 6. Kinetics of CEA concentration in 12 patients with relapse not associated with a rise in CEA level. A few moderate and transitory rises may be noted, but these were of no significance to possible metastatic development.

DISCUSSION

More than 50% of the relapses in our series of patients were announced by a significant rise in CEA level, often several months before manifestation of clinical symptomatology. Several previous reports indicate comparable results: Coombes [5] found that 10 out of 22 patients experiencing relapse had a high CEA level some months before the clinical signs appeared; likewise, Haagensen [6] noted that in 17 out of 48 relapses there was a rise in CEA at the same time as or before the clinical signs; and Tormey [7] and Falkson [8] reported comparable findings, although based on small numbers of patients.

It would thus appear that serial CEA assays are a good method of detecting breast cancer relapses, often more readily than other diagnostic means, regardless of the assay method used, whether direct as in our study or with perchloric extraction. Nevertheless, care must be taken in interpreting results; in effect, the initial rise in CEA level is generally slight,

and it is thus important to know whether or not it is significant. In this respect, as Martin has suggested [9], it would seem useful to consult a precision graph to ensure that a rise is not simply due to variability in the assay method. Moreover, a significant rise does not necessarily signal a relapse and must be confirmed by one or more additional assays. In fact, a transitory rise may be associated with an intercurrent benign inflammation or with smoking before the serum sample is taken [10].

Having determined that a persistent rise in CEA level most often announces a relapse clinically confirmed several months later, we deemed it advisable to compare CEA with other possible markers of cancer development. The present study indicates no correlation between a change in CEA level and that of haptoglobin, one of the biological parameters of inflammation. CEA also seems to be a better marker of osseous metastatic spread than is alkaline phosphatase, despite the small number of cases studied. There is also question as to the usefulness of assessing CEA during chemotherapy when the initial level before treatment is normal. Under our conditions for recruiting subjects, the first assay was in most cases performed after surgery and/or irradiation. In 2 cases, however, the level showed an early rise 3–5 months before clinical signs of relapse, despite a normal level before treatment.

Our findings confirm those reported by Tormey [7] in showing that CEA level rises most often in cases of liver, bone or node metastases, whereas it remains normal in most cases of local recurrence.

If it may be granted that CEA is a sensitive marker permitting detection before other diagnostic means of more than 50% of relapses, it is still necessary to consider what the therapeutic consequences of a significant and persistent rise in CEA level might be when there are no clinical signs of recurrence. In effect, one of the problems which the clinician must cope with when following the course of malignant tumors for which he has a sensitive biological marker at his disposal is the following: In the absence of other paraclinical confirmations, must the confirmed rise in a marker entail implementation of immediate systematic treatment?

In certain sites (colon, ovaries) a surgical second look may be considered [9], which could lead to exploration and effective surgical resection. On the other hand, in breast cancer such an approach is not feasible, and it may be preferable to resume treatment or to alter the hormonotherapy and/or chemotherapy treatment in progress according to changes signalled by the marker used, e.g., CEA, as in the present study. This is shown in Fig. 3 where prescription of a treatment involving anti-estrogens permitted a marked decrease in CEA level which had been confirmed as high and clearly suggestive of metastatic spread.

Certainly, only the accumulation of data and the passage of a sufficient period of time will determine whether or not this therapeutic approach is justified, in terms of improved survival of patients given early treatment in comparison with those treated only when metastatic development is evident.

CONCLUSION

Our study indicates that among high risk breast cancer patients more than 50% of relapses are associated with a significant rise in CEA level, with this rise appearing to be a sensitive means of detection before other diagnostic means in 40% of the relapses. Among sites of metastasis, liver and/or bone are most often associated with a rise in CEA level. However, the long-term effect of detection on therapy and patient survival remains to be defined.

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