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*Guest Editorial**

CEA (Carcinoembryonic Antigen): Its Role as a Marker in the Management of Cancer**

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Summary. A Consensus Development Conference was held at the National Institutes of Health from September 29–October 1, 1980, to address issues concerning the role of carcinoembryonic antigen (CEA) as a marker in the management of cancer. The panel met following formal presentations and discussions to assess the issues based on the evidence presented. These issues included: Should CEA be used in cancer screening? Is CEA helpful in cancer diagnosis? What does CEA tell about the extent and outcome of cancer? Is CEA helpful in monitoring cancer treatment? This paper constitutes the panel's findings.

Key words: Carcinoembryonic antigen – Tumor marker – Cancer management

Introduction

Human neoplasms may produce and release into the circulation a variety of substances collectively referred to as *tumor markers*. The oncofetal antigens comprise one particular group of markers, of which the carcinoembryonic antigen (CEA) has been the most widely studied.

CEA is a glycoprotein of about 200,000 molecular size. It is expressed in significant amounts during embryonic life, especially by the large intestine, and postnatally by carcinomas arising from this site. CEA can be released by these tumors into the circulation to cause raised levels which may be measured by sensitive

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radioimmunoassay and related techniques. Such methods have, however, demonstrated that small amounts of CEA are also present in the normal adult large intestine and in the circulation of healthy subjects.

Subsequent investigations have revealed that many epithelial-derived tumors at other sites may also express CEA and be associated with elevated circulating blood levels. Thus, it may be that the assay of plasma CEA has protean applications in oncology.

The Consensus Development Panel and members of the audience considered evidence to address the following questions:

1. Should CEA be used in cancer screening?
2. Is CEA helpful in cancer diagnosis?
3. What does CEA tell about the extent and outcome of cancer?
4. Is CEA helpful in monitoring cancer treatment?

Plasma CEA Levels in Health and Disease

Using the presently available radioimmunoassay, 2.5 ng/ml is stated to be the upper limit of normal for plasma CEA levels. Values in excess of 2.5 ng/ml may be found in association with cancers, in particular those of the gastrointestinal tract, pancreas, ovary, lung, and breast. Similarly raised CEA levels may, however, be detected in cigarette smokers, in patients with benign neoplasms, and in 15–20% of subjects with inflammatory disorders, such as ulcerative colitis, Crohn's disease, pancreatitis, liver disease, and pulmonary infections. Thus, raised plasma CEA values are not specific for cancer, although very high levels (e.g., above 20 ng/ml) are highly suggestive of malignancy. It is important that serial assays of CEA be used in reaching a clinical judgement, and not any single determination. The panel believes that each laboratory performing CEA assays should establish its own "normal" range. The recommended upper level of "normal" (2.5 ng/ml) in the population requires additional evaluation. Values cited in this document are based on the only radioimmunoassay commercially available at the time of the conference, the Hoffmann-La Roche assay. Other assay systems may give different results

Conclusions and Recommendations

After listening to and discussing the evidence, the Panel reached the following conclusions:

1. Should CEA be Used in Cancer Screening?

As indicated above, studies to date have revealed a major overlap in the distribution of plasma CEA values in subjects with inflammatory diseases and benign and malignant tumors of the gastrointestinal tract and of other sites, including breast, bronchus, urothelium, ovary, uterus, and cervix. Therefore, the plasma CEA assay does not possess the sensitivity (true-positive rate) or the specificity (true-negative rate) required to discriminate between localized malignant tumors and benign disorders.

Consequently, these data, together with the fact that raised CEA levels occur in smokers, vitiate the use of plasma CEA assays in the screening of the asympto-

matic population to detect neoplastic disease. The use of CEA to assist with the surveillance of so-called high-risk groups, in whom CEA-producing tumors may develop, remains to be established.

2. Is CEA Helpful in Cancer Diagnosis?

Few prospective studies have been effected with the aim of determining whether the availability to clinicians of a plasma CEA result would help in confirming a suspected malignancy in symptomatic patients. In addition, the caveats with respect to cancer specificity which limit the CEA test's applicability for screening (namely, that raised levels occur with smoking, non-neoplastic diseases, and benign tumors) are also pertinent with respect to assisting in reaching a diagnosis in a symptomatic population.

Therefore, we cannot recommend, based on the presently available data, that CEA be used independently to establish a diagnosis of cancer. However, in a patient with symptoms, a grossly elevated value, greater than five to ten times the upper limit of the reference normal range for that particular laboratory, should be considered strongly suggestive for the presence of cancer in that particular patient. In this situation, further diagnostic efforts to establish the presence or absence of cancer are indicated.

3. What Does CEA Tell About the Extent and Outcome of Cancer?

Many workers have shown that preoperative plasma CEA levels correlate with the clinical stage of disease in several tumor types. Patients with colorectal or possibly bronchial carcinomas whose preoperative CEA levels are at the lower end of the spectrum have better survival rates than patients whose levels are in excess of 10 ng/ml.

It should be remembered, moreover, that the correlation between increasing plasma CEA levels and progressive cancer is not always perfect and that a normal CEA cannot be taken as evidence of localized disease or remission. About 15–20% of patients with proved malignancies never have elevated plasma levels. Such false negatives may be related to the degree of tumor differentiation. Poorly differentiated colorectal carcinomas, e.g., tend to be associated with a reduced proclivity for CEA expression and release.

On the basis of the available data, we recommend that a preoperative plasma CEA value be obtained in patients with either colorectal or bronchial carcinomas and be used as an adjunct to clinical and pathologic staging methods.

4. Is CEA Helpful in Monitoring Cancer Treatment?

The regular and sequential assay of plasma CEA is the best presently available noninvasive technique for postoperative surveillance of patients to detect disseminated recurrence of colorectal cancer. As a monitor of colorectal cancer, CEA has been found to be elevated when residual disease is present or is clinically progressing. Following complete surgical removal of a colorectal malignancy, an elevated plasma CEA value should usually return to normal by six weeks. The failure to observe a reduction of a previously elevated preoperative CEA titer strongly indicates the presence of residual tumor. It is also possible to demonstrate in a substanial

number of patients that CEA becomes significantly elevated before metastatic disease can be detected by clinical or other diagnostic measures. This information can be best achieved by obtaining plasma samples for CEA assay preoperatively, 4–6 weeks postoperatively, and thereafter at regular intervals as an integral component of overall patient follow-up. While slowly rising levels may be more indicative of local recurrence, rapidly rising values reaching very high levels, usually in excess of 20 ng/ml, are found most often with hepatic and osseous metastases.

For patients with metastatic tumor, the CEA assay may complement standard clinical measurements of tumor response to therapy. However, as in the case of other clinical laboratory tests, there are examples of discordance between the observed change in tumor mass and the corresponding CEA values. In patients with advanced unmeasurable tumor, especially colorectal carcinoma, CEA assays may offer the only index to measure changes in tumor burden. Although definite criteria to aid in deciding whether to continue or alter therapy in patients with unmeasurable tumor, based on serial CEA determinations, are not established, it appears that a steadily, markedly rising titer is indicative of a poor therapeutic response. In such circumstances, each physician should make an individual decision whether CEA monitoring will be of clinical value in the management of a particular patient.

It is important to remember that raised values, due to various causes, such as smoking, intercurrent infection, etc., can be seen in patients where the tumor is clinically stable and that decreasing CEA values are not invariably a sign of successful therapy. Furthermore, a proportion of patients with recurrent or advanced colorectal cancer may not show elevated plasma CEA values.

The role of CEA in the postoperative and therapeutic monitoring of patients with other types of cancer, such as pancreatic, gastric, and gynecologic neoplasms, is less convincing than it is for colorectal cancer. In patients with metastatic breast cancer or lung cancer, especially small-cell carcinoma, and significant CEA elevations, changes in CEA titers may be of value in reflecting response to chemotherapy. More studies are required to evaluate the role of CEA determinations for initiating or changing therapy in tumor types other than colorectal cancer.

The Panel would like to stress the view that the clinical utility of a tumor marker may be related to the efficacy of a therapeutic regimen. Where earlier recognition of disease progression is not accompanied by appropriate therapy, no benefit is gained. On the other hand, as more successful treatments for the major tumor types become available, CEA and other tumor markers will be more useful in the management of cancer.

Additional Needs

The Panel has identified several areas for future study which should improve the clinical utility of the CEA assay: the improvement of assay methodology; the evaluation of monoclonal antibodies to CEA for improving assay specificity; the establishment of a laboratory quality control system using a CEA standard preparation; the clinical study of CEA in combination with other markers; the diagnostic role of CEA in biologic fluids other than plasma; the individual and collective comparison of CEA with other specific diagnostic modalities; the estimation of tumor CEA content in relation to plasma CEA values; and the study of the pathophysiology and metabolism of CEA.