MEDICAL PRACTICE

Consensus in Medicine

Carcinoembryonic antigen: its role as a marker in the management of cancer

SUMMARY OF AN NIH CONSENSUS STATEMENT

A consensus development conference was held at the National Institutes of Health on 29 September-1 October 1980 to address issues concerning the role of the carcinoembryonic antigen (CEA) as a marker in the management of cancer.

NIH consensus development conferences bring together biomedical research scientists, practising physicians, consumers, and others with special interest or knowledge in an effort to reach general agreement on the scientific evaluation of a medical technology. That technology may be a drug, device, or laboratory, medical, or surgical procedure. For this consensus conference, the members of the panel were limited to biomedical and clinical investigators actively working in the field, clinically involved in patient care, and familiar with the technology under assessment. The panel met after formal presentations and discussions to assess the issues based on the evidence presented. This summary is the result of its deliberations.

Introduction

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

CEA is a glycoprotein of about 200 000 molecular size. It is expressed in appreciable amounts during embryonic life, especially by the large intestine, and after birth by carcinomas arising from this site. CEA can be released by these tumours into the circulation to cause raised concentrations, which may be measured by sensitive radioimmunoassay and related techniques. Such methods have, however, shown that small amounts of CEA are also present in the normal adult large intestine and in the circulation of healthy subjects.

Subsequent investigations have shown that many epithelial derived tumours at other sites may also express CEA and be associated with raised circulating blood concentrations. Thus, the assay of plasma CEA may have protean applications in oncology.

The consensus development panel and members of the audience considered evidence to address the questions given below.

Plasma CEA concentrations in health and disease

By using the presently available radioimmunoassay 2·5 μg/l is stated to be the upper limit of normal for plasma CEA concentrations. Values over 2·5 μg/l may be found in association with cancers, in particular those of the gastrointestinal tract, pancreas, ovary, lung, and breast. Similarly raised CEA concentrations, may, however, be detected in cigarette smokers, in patients with benign neoplasms, and in 15 to 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 concentrations (for example, above 20 μg/l) are highly suggestive of malignancy. It is important that serial

Members of the consensus development panel were:
Dr David M Goldenberg (chairman), University of Kentucky Medical Center, Lexington; Dr A Munro Neville (rapporteur), Ludwig Institute for Cancer Research, Sutton, Surrey, UK; Dr Anne C Carter, State University of New York School of Medicine, New York; Dr Vay Liang W Go, Mayo Clinic, Rochester, Minnesota; Dr Edward Douglas Holyoke, Roswell Park Memorial Institute, Buffalo, New York; Dr Kurt J Isselbacher, Massachusetts General Hospital, Boston; Dr Philip S Schein, Vincent T Lombardi Cancer Research Center, Georgetown University Medical Center, Washington, DC; Dr Morton Schwartz, Memorial Sloan-Kettering Cancer Center, New York. The conference organisers were Dr K Robert McIntire and Mr Louis P Greenberg, National Cancer Institute, Bethesda, Maryland.

assays of CEA be used in reaching a clinical judgment 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 μg/l) 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.

After listening to and discussing the evidence, the panel reached the following conclusions.

(1) Should CEA values be used in cancer screening?

As indicated above, studies have shown a major overlap in the distribution of plasma CEA values in subjects with inflammatory diseases and benign and malignant tumours 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 localised malignant tumours and benign disorders.

These data, together with the fact that raised CEA concentrations occur in smokers, therefore vitiate the use of plasma CEA assays in the screening of an asymptomatic population to detect neoplastic disease. The use of CEA to help with the surveillance of so-called high-risk groups, in whom CEA-producing tumours may develop, remains to be established.

(2) Are CEA values helpful in diagnosing cancer?

Few prospective studies have been performed 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 values occur with smoking, non-neoplastic diseases, and benign tumours—are also pertinent with respect to helping in reaching a diagnosis in a symptomatic population.

Therefore we cannot recommend on the basis of presently available data that CEA values be used independently to establish a diagnosis of cancer. In a patient with symptoms, however, a grossly raised value, greater than 5-10 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 these circumstances further diagnostic efforts to establish the presence or absence of cancer are indicated.

(3) What do CEA values suggest about the extent and outcome of cancer?

Many workers have shown that preoperative plasma CEA concentrations correlate with the clinical stage of disease in several types of tumour. Patients with colorectal or possibly bronchial carcinomas whose preoperative CEA concentrations are at the lower end of the range have better survival rates than those whose concentrations are over 10 μg/l.

It should be remembered, however, that the correlation between increasing plasma CEA concentrations and progressive cancer is not always perfect and that a normal CEA value cannot be taken as evidence of localised disease or remission. About 15 to 20% of patients with proved malignancies never have raised plasma concentrations. Such false-negatives may be related to the degree of tumour differentiation. Poorly differentiated colorectal carcinomas, for example, 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 pathological staging methods.

(4) Are CEA values helpful in monitoring treatment for cancer?

The regular and sequential assay of plasma CEA is the best presently available non-invasive 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 raised when residual disease is present or clinically progressing. After complete surgical removal of a colorectal malignancy a raised plasma CEA value should usually return to normal by six weeks. Failure to observe a reduction in a previously raised preoperative CEA titre strongly indicates the presence of residual tumour. In a substantial number of patients CEA values also become significantly raised before metastatic disease can be detected by clinical or other diagnostic measures. This information can best be achieved by obtaining plasma samples for CEA assay before operation, four to six weeks after operation, and thereafter at regular intervals as an integral component of overall patient follow-up. While slowly rising values may be more indicative of local recurrence, rapidly rising values reaching very high concentrations, usually over 20 μg/l, are found most often with hepatic and osseous metastases.

For patients with metastatic tumour, the CEA assay may complement standard clinical measurements of tumour response to treatment. As in the case of other clinical laboratory tests, however, there are examples of discordance between the observed change in tumour mass and the corresponding CEA values. In patients with advanced unmeasurable tumour, especially colorectal carcinoma, CEA assays may offer the only index of changes in the tumour burden. Although definite criteria to help in deciding whether to continue or change treatment in patients with unmeasurable tumour, based on serial CEA determinations, are not established, it appears that a steadily, sharply rising titre indicates a poor therapeutic response. In such circumstances each doctor 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, may be seen in patients where the tumour is clinically stable and that decreasing CEA values are not invariably a sign of successful treatment. Furthermore, some patients with recurrent or advanced colorectal cancer may not show raised plasma CEA values.

The role of CEA values in the postoperative and therapeutic monitoring of patients with other types of cancer, such as pancreatic, gastric, and gynaecological 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 increases in CEA concentrations, changes in CEA titres may be of value in reflecting response to chemotherapy. More studies are required to evaluate the role of CEA determinations for initiating or changing treatment in tumour types other than colorectal cancer.

The panel would like to emphasise that the clinical usefulness of a tumour marker may be related to the efficacy of a therapeutic regimen. When earlier recognition of disease progression is not accompanied by appropriate treatment no benefit is gained. On the other hand, as more successful treatments for

the major types of tumour become available, CEA and other tumour 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 usefulness of the CEA assay: the improvement of assay methods; 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 biological fluids other than plasma; the individual and collective comparison of CEA with other specific diagnostic methods; the estimation of tumour CEA content in relation to plasma CEA values; and the study of the pathophysiology and metabolism of CEA.

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For Debate . . .

Changing patterns of psychiatric care

P WILLIAMS, A CLARE

By the end of the 1960s it had become clear that the general-practitioner services in Britain were coping with the overwhelming proportion of the total amount of psychiatric morbidity within the community, leaving only a small and atypical proportion to the specialised psychiatric services.[1 2] Shepherd and his colleagues championed the strengthening of the "therapeutic role" of the general practitioner to enable him to meet this challenge, a strategy since endorsed by the World Health Organisation.[3] Other voices, however, particularly transatlantic ones, were raised, both at the time and since, in favour of improving accessibility to psychiatrists and of a corresponding increase in the number of specialist psychiatrists.[4-6] Developments in general practice in Britain over the past ten years[7] reflect the extent to which the role and the scope of general-practice management of psychiatric ill health has developed. There has been surprisingly little comment, however, concerning the impact of changes within specialised psychiatry on patterns of referral and management within the specialised and primary care services.

The years 1970-5 witnessed a dramatic increase in psychiatric manpower—the number of consultant psychiatrists rising by 28%, non-consultant psychiatric staff by 35%, clinical psychologists by 64%, and psychiatrically trained nurses by 31%. This expansion affords a useful opportunity to examine the assumption, made at the end of the 1960s, that expanding the specialised services would result in a shift of some of the burden of psychiatric management from the primary care to the specialised services. The expansion occurred at a time when the total number of psychiatric beds was contracting, and psychiatrists were becoming more aware of the social and community aspects of their work.[8] The scene was set, therefore, for a shift from general practitioner to psychiatrist. Has it happened?

There are three possible answers to this question: (1) Nothing has happened and the situation remains unaltered. The same amount of work is being done by the same practitioners with the same amount of patients (the "unchanged" hypothesis). (2) There has been no appreciable change in the number of patients being managed by psychiatrists but more treatment (in the nature of support, time, and techniques) is being provided for each one (the "intensive" hypothesis). (3) Psychiatrists are actually seeing more patients and hence are managing a greater proportion of the morbidity than before the expansion of psychiatric manpower (the "extensive" hypothesis).

To test these hypotheses we investigated the changing pattern of psychiatric care during 1970-5.

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Method

Relevant data for England and Wales for the years 1970-5 were extracted from the following sources: *Facilities and Services of Mental Illness and Mental Handicap Hospitals in England*, *Inpatient Statistics from the Mental Health Enquiry for England*, and *Health and Personal Social Services Statistics for England*. The data presented here relate only to mental illness hospitals and units and not to mental handicap facilities, but include units in general and teaching hospitals.

Results

Table I shows all outpatient and all day-patient attendances at, and all admissions to, mental illness hospitals and units in England for the relevant years. The relevant findings are as follows:

(1) The total number of outpatient attendances (NB not patients) increased by 11-12%: the average number per consultant psychiatrist decreased by 20%.

(2) The total number of day-patient attendances (NB not patients) increased by 55%; the average number per consultant psychiatrist peaked in 1973 (+14%) but fell back to +11% by 1975.

(3) The total number of inpatient admissions did not change appreciably, so that the average number per consultant psychiatrist decreased by 27%.

Table II shows new referrals to outpatient facilities and day hospitals, and first admissions to mental hospitals and units. The relevant findings are as follows:

(1) The number of new referrals to outpatient clinics remained more or less unchanged from 1970 to 1974, but the rate per consultant psychiatrist decreased by 21%. Fewer new patients were referred in 1975 than in any of the previous five years.

(2) New referrals to day hospitals increased by just under 50%. The rate per consultant psychiatrist peaked in 1973 (+20%) and then fell to +5% in 1975. At the same time, the number of patients discharged from hospital to attend as day patients increased by 43%.