February 10, 1991

TUMOR MARKER MONITORING

Herbert A. Fritsche, Ph.D.

DR. FRITSCHE: It is a pleasure to be here today, and I want to thank Doctors Schwartz and Fidelino for this opportunity to discuss what remains a controversial topic some 20 years after the modern era of tumor markers began with the introduction of the CEA test.

The other speakers have pointed out that our current tumor marker tests are tumor-associated substances, and what we really need for diagnostic purposes are tumor-specific substances. Hopefully, these can be identified from the products rearranged or mutated oncogenes and later I'll present one example of such a tumor-specific oncoprotein.

A tumor-associated substance becomes a tumor marker test when it can provide information in one or more of the following areas:

a) Establishing the diagnosis

b) Defining the stage of the disease

c) Assessing prognosis

d) Selecting therapy

e) Evaluating patient response to therapy

f) Monitoring for disease recurrence after successful treatment

Today, I will extend some of the observations that Dr. Bates just made, and go into some new areas as well. But, first, I'd like to review the goals for patient monitoring as shown on the first slide.

(SLIDE)

Patient Monitoring Goals

Enhance patient care

- Extend survival time
- Improve quality of survival

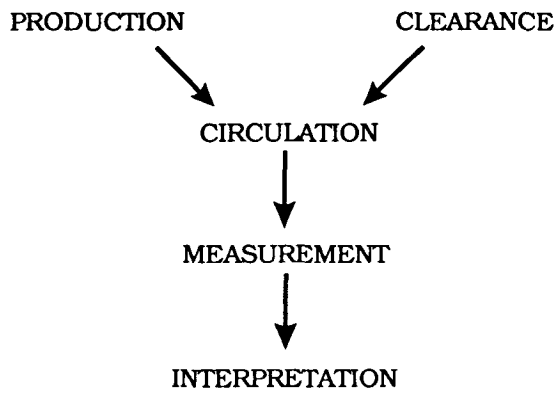
Reduce cost of care

- Avoid unnecessary clinical procedures
- Substitute for more costly procedures
- Select most effective treatment(s)

An obvious goal is to enhance patient care. We have to remember that tumor markers are not treatments and that the relevance of tumor markers for particular cancers are only as good as the treatments allow them to be. The other speakers have made that observation also. So how can tumor markers enhance patient care? Hopefully, they can extend survival time and improve the quality of that survival by optimizing the use of treatment programs.

The tumor markers that we have in routine use today are: prostatic acid phosphatase (PAcP), prostate specific antigen (PSA), alpha fetoprotein (AFP), chorionic gonadotrophin (HCG), carcinoembryonic antigen (CEA), and CA 125. Both PSA and CA 125 are useful diagnostic aids for prostate and ovarian cancer, respectively. Tumor markers have only limited value in disease staging, and that is to keep from understaging a patient, as it is highly unlikely that a patient with a significantly elevated tumor marker value has only local disease. This is perhaps the most important role today for prostatic acid phosphatase. In some staging systems when PAcP is elevated the patient is considered to have metastatic disease. Serum tumor markers have an even more limited use for establishing prognosis. In fact, the only serum marker to have prognostic value that I am aware of is the serum beta-II microglobulin test in patients with multiple myeloma. This is because the β2M measured renal function as well as tumor mass, and reflects both of those independent prognostic factors. But the use of the β2M for patient monitoring is limited, because it can only provide an assessment of tumor burden when renal function is normal. For the selection of therapy, the only tumor marker tests that we have are tissue tests such as estrogen and progesterone receptor proteins. The most effective use for tumor markers is in monitoring therapy, and for those patients who have been treated effectively, monitoring for recurrence of the disease. Now how can we insure the accurate interpretation of tumor marker values when they are used to monitor the clinical status of a patient?

(SLIDE)



First, we need a highly sensitive and specific measurement technique to get an accurate assessment of the serum concentration of the marker. The amount of the marker in the circulation is regulated by production and clearance factors. Not all tumor cells have the same propensity for manufacturing and secreting a tumor marker substance. The production factors are modulated by various clearance factors. Dr. Rose talked about immune clearance of some markers, and host response clearance was brought up by another speaker. But, liver and kidney function are probably the two most important modulators of the tumor markers. The apparent half-life of the marker reflects the net effect of the production and clearance factors and must be considered in order to avoid false interpretation of tumor marker changes.

The next slide emphasizes other considerations necessary for patient monitoring.

(SLIDE)
Patient Monitoring Considerations

1. Establish pre-therapy baseline or trend.
2. Perform on a regular and frequent basis.
3. Interpret change using established criteria.
4. Insure test precision remains constant with no lot-to-lot bias.

After the pre-therapy baseline of a marker is established, the monitoring test should be performed on a regular and frequent basis. How frequent will depend upon the type of cancer, the therapy, and the half-life for the marker. We must interpret changes of the marker in terms of established criteria, and insure that the test precision remains constant so that tumor marker changes are not due to "lot-to-lot" variation of the test method. While most of our patient monitoring experience has been developed with CEA, much of this knowledge can be directly applied to other markers as well.

Some ten years ago, a consensus conference assessed the clinical value of CEA at that time. It was agreed that the CEA test should not be used for cancer screening or independently to establish a diagnosis. However, CEA serial monitoring was acknowledged to be the best technique for post-operative surveillance of the colorectal cancer patient. The next slide shows the utility of the CEA test for directing "second-look" surgeries for colorectal cancer patients.

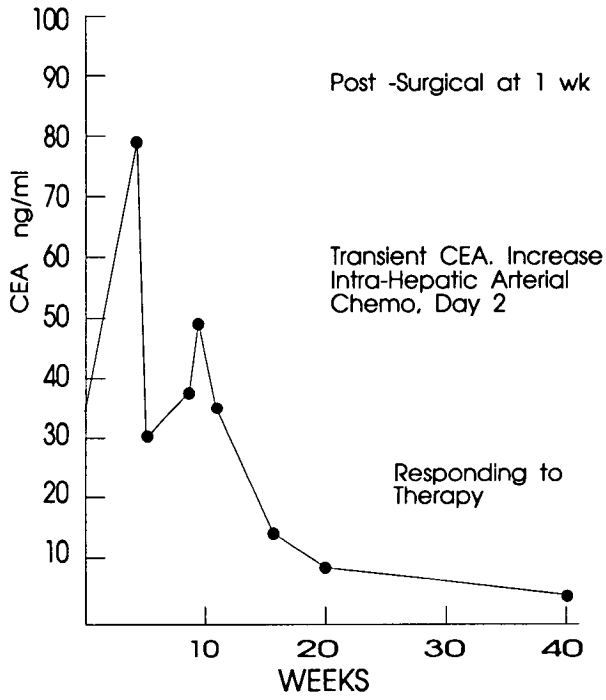
(SLIDE)
CEA and Second-Look Surgery in Colorectal Cancer*

	CEA Directed	Non CEA Directed
Number of Patients	21/69 (30%)	48/69 (70%)
True Positive	19/21 (90%)	40/48 (83%)
Complete Resection	12/19 (63%)	13/40 (33%)
Five Year Survival	48%	30%

* Chu D, et al. *J Tumor Oncol* 1987; 2:27-39.

In this study, 69 patients were identified for second-look surgery. Twenty-one, or about 1/3 of the patients, had surgery performed on the basis of sequentially rising CEA values over a period of time. The other 48 surgeries were non-CEA directed. Recurrent disease was found in about 90% of both groups, but there was a better complete resection rate for the CEA-directed versus the non-CEA directed group. And, there was a slight five-year survival advantage for the CEA-directed surgery group.

(SLIDE)



This slide shows the serial CEA pattern of a colorectal cancer patient with liver metastasis. The post surgical rise at A is expected and is due to the healing process. The CEA value does not return to normal, indicating the presence of residual disease. This patient was subjected to intrahepatic arterial chemotherapy, responded to that chemotherapy, and CEA demonstrated a chemotherapy induced rise at B. This rise may be called a false-positive rise, but actually is a "paradoxical" increase. The CEA rise is due to increased production resulting from tumor cell cytotoxicity. Later, the CEA values drop, eventually down to normal, but this patient never achieved a complete remission. This shows that a negative CEA test does not mean that all of the cancer has been eradicated.

Now, let's discuss the use of CEA in monitoring breast cancer patients undergoing chemotherapy. In a recent paper (*Cancer* 1990; 65:193-199), Kennedy and Kiang described tumor marker patterns given by these patients. In patients who have tumor progression, the marker value continuously increases over time. In those patients who respond to therapy, there may be a paradoxical increase followed by the marker value falling. The values may fall, but remain elevated as in a partial remission, or the values may fall below the upper limit of normal. Remember that a negative CEA value does not necessarily indicate a complete remission.

(SLIDE)

CEA as a Monitor of Breast Cancer

Mughal, et al. *JAMA* 1983; 249:1881.

- Serum CEA elevated in 50% with stage 4 disease (N=167).
- Significant decrease in 94% who responded to therapy (66/70).
- Duration of response was longer (22 mo. vs 9 mo.) for patients whose values dropped to normal values.
- Significant CEA increase was observed in 87% (27/37) of patients who developed progressive disease (preceded other clinical indication of recurrence in 24/27).
- Median lead time was 3 months, range of 1-13 mo.

This slide summarizes our experience with CEA in breast cancer and shows that it can accurately reflect the clinical course of the disease. I should point out that serum marker changes should always be interpreted according to defined criteria as shown on the next slide.

(SLIDE)

Criteria for Defining a Clinically Significant Change in Marker Values

A. Initially Normal Value:

Rise to above the upper limit of normal and demonstrate a minimum increase of 100% above the previous value.

EXAMPLE: 5.0 → 10.0 ng/ml.

B. Demonstrate at least a 25% increase in each of two (2) serial values.

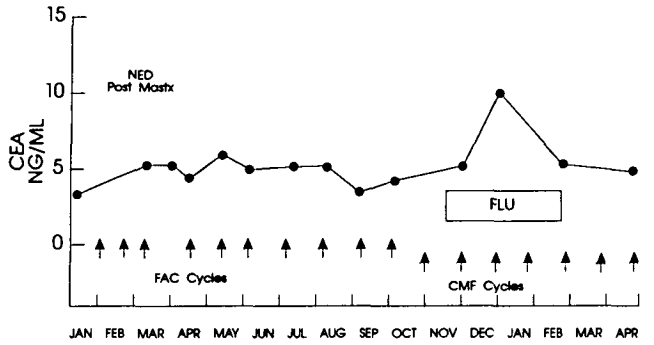
EXAMPLE: 10.0 → 13.0 → 15.0 ng/ml.

Demonstrate a 50% increase from the previous value.

EXAMPLE: 20 → 30 ng/ml.

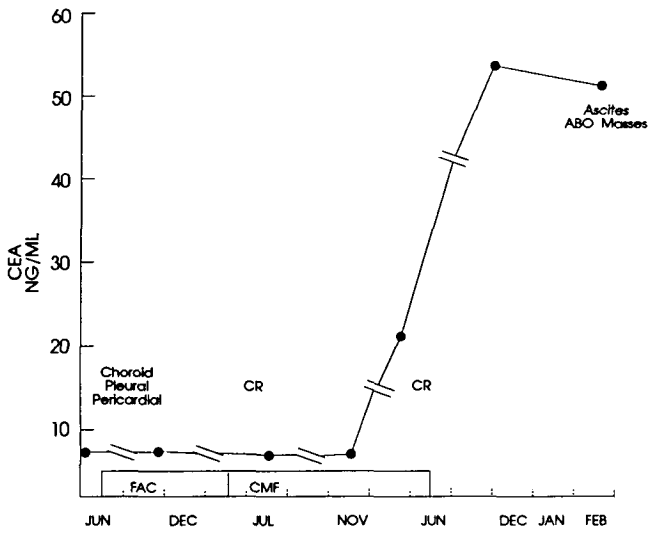
Similar criteria should be developed for all serum markers. These objective criteria take into account the precision of assays and the biologic variation of the markers and helps the laboratory develop appropriate quality assurance measures.

(SLIDE)



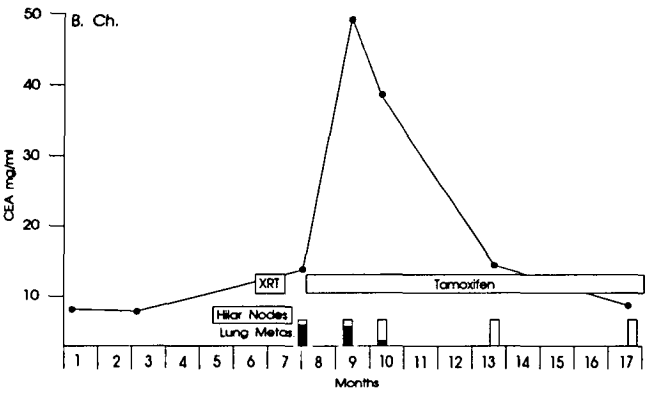
This slide shows the long-term precision that required for monitoring tests. In this particular case, the serial values are within 1.5 ng/ml over a period of 11 months. When a significant change occurs, it can be easily noted. This false-positive rise related to this acute disease is not difficult to recognize, as there usually is some other sign or symptom. If the marker rise cannot be correlated with another disease process, the test should be repeated on a freshly collected serum sample before anything is done to the patient or before any other clinical workup is attempted. If the marker rise cannot be explained, it may be necessary to wait for another half-life or two to pass and repeat the test. In most acute, inflammatory diseases the marker rise will be transient, and the values will return to normal after the inflammatory phase of the disease. If the rise cancer related, the marker value will continue to rise over time.

(SLIDE)



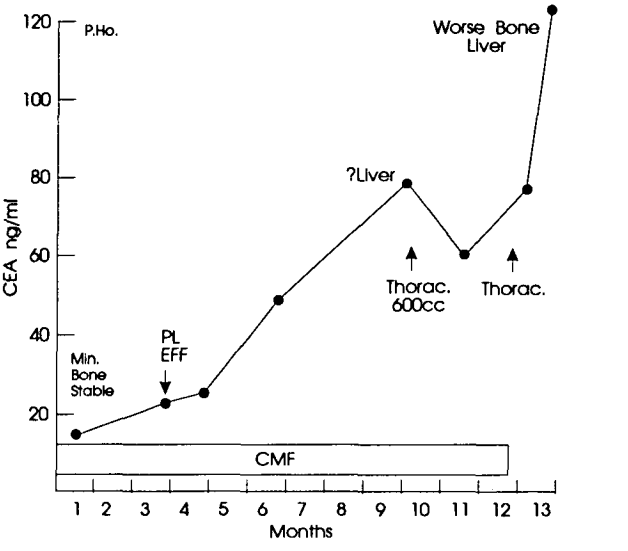
This slide shows such a marker value change that is related to cancer. We see CEA values consistently 5 ng/ml until this sudden increase up to 20 ng/ml. The patient is still noted to be in complete remission. Later an abdominal mass developed with considerable increases in the CEA value. In this particular case, CEA provide an opportunity to initiate therapy two months before clinical evidence of disease recurrence.

(SLIDE)



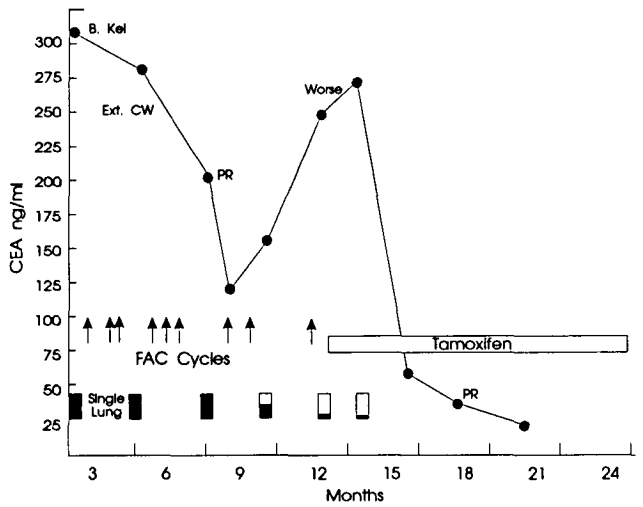
This slide shows the CEA pattern of a patient responding to chemotherapy who demonstrated the paradoxical increase. This paradoxical increase, where the CEA or marker value is increasing with response to therapy, is an indication that the tumor cells are synthesizing the marker, but not secreting it into the circulation. With cell death, the marker substance is suddenly released into the circulation. The CEA values eventually return to normal with the complete remission.

(SLIDE)



This slide shows a rapidly increasing CEA value from 80 to 120 ng/ml over a period of two weeks, resulting from increased liver disease and decreased clearance. In this case, the elevated CEA is due to increased CEA increased production from the progressive disease, and the decreased clearance due to impaired liver function.

(SLIDE)



For patients with multiple metastatic sites, tumor marker interpretations may be more difficult. This CEA pattern was obtained from a patient who had lung metastasis and a chest wall recurrence. The patient was treated and there was an initial decrease in the tumor marker value. The chest wall lesion showed a partial remission, but there was no response by the lung lesion until 9-12 months later. Initially then, we see no significant change in the lung, but significant changes in the chest wall lesion. Then the chest wall lesion starts to progress. Finally, both metastatic sites responded when the patient was treated with hormonal therapy. So, one could argue that the CEA was not reflecting the clinical course of the patient. But, we must remember to keep the entire patient in perspective, and be aware that each of the metastatic sites may not be responding to the therapy in the same way.

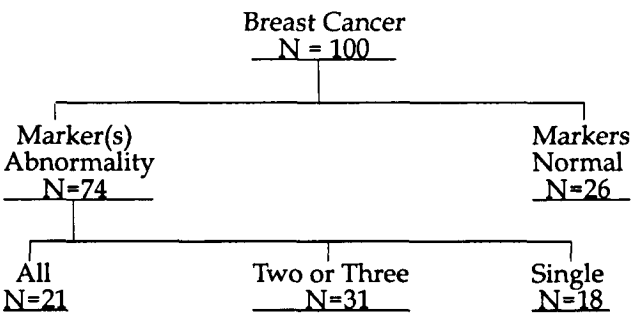
The experience with the multiple metastatic sites leads us into a discussion of multiple markers. As Dr. Bates and Dr. Schwartz have indicated, the best combination of markers we have today are alpha-fetoprotein and HCG for non-seminomatous germ cell tumors. The problem with using multiple markers is that they sometimes give discordant results and when this happens, what do you do? In the case of alpha-fetoprotein and HCG, we have enough experience in the follow-up of non-seminomatous germ cell tumors to accurately interpret discordant marker values. But as we expand to the application of other markers to other cancers, the interpretation of discordant values may be a problem. I think the only way we can handle the confusion is by following the patient, obtaining more experience with the markers, and not making an immediate clinical decisions on the basis of marker values alone. So, what other tumor marker panels do we have developing today? The next slide shows a list of the breast cancer mucins which can complement the CEA test in breast cancer monitoring.

(SLIDE)
Breast Cancer Mucins

CA15-3	115D8/DF3	Centocor
BCM	M 85	Abott
Tru-Quant BR	M 27.29	Biomira
MCA	B 12	Roche
CA 549	BC4E549	Hybritech
CAM 26	M 26	Sanofi

These breast cancer mucins are not specific for breast cancer, but have application to other solid tumors as well. CA15-3 is the most well-known of these tumor mucins, but the other mucin tests appear to be just as good as the CA 15-3. It has become obvious that we don't need all of these mucin markers.

(SLIDE)
CEA And Breast Cancer Mucins
(M26, M29, CA 15-3)



Conclusions

A. No single marker is sufficient.

B. Most frequently elevated 2 markers: M29 and CA15-3.

C. All four markers are not required.

As shown on this slide, we have found that with a panel consisting M26, M29, CA 15-3, and CEA, about 75% of metastatic breast cancer patients showed marker abnormalities. In this group of patients, the best combination of two markers was M29 and CA 15-3.

Another new breast cancer marker may be the neu oncogene related protein (NRP). This is the membrane receptor for a yet undefined growth factor. Serum NRP appears to be elevated in 20-30% of metastatic breast cancer patients with a false positive rate of 20-25% in benign breast disease. So a useful breast cancer panel might consist of CEA, CA 15-3 (or equivalent test) and NRP.

An important area that I don't have time to go into today is the use of prognostic tests in early stage breast cancer, to supplement the estrogen and progesterone receptor protein. The most likely new candidates are the EGF receptor (especially in ER/PR negative breast cancer patients), NRP, a proteolytic enzyme called cathepsin D, insulin-like growth factor receptor, heat shock proteins, anti-oncogene product P53 and the estrogen-related protein, PS2. Urinary gonadotropin peptide (UGP) may be a complementary test to the CA 125 in ovarian adenocarcinoma. UGP is a peptide sequence of the core section of the beta-subunit of HCG. It consists of amino acid residues 6-40 linked by disulfide bridges to residues 55-92. Its half-life is 0.06 hours, so it cannot be measured in serum.

Now, just a few words about early diagnostic markers such as the BCR-ABL protein. It is the product of the recombined genes from chromosomes 9 and 22, a translocation in which a chimeric message results from the recombined Philadelphia chromosome. This BCR-ABL protein is now thought to be key in the development of chronic myelogenous leukemia, and its presence should only occur in this situation. If we can define similar chromosome translocations for solid tumors, it will be feasible to develop diagnostic tumor marker tests. That will not be as simple as it sounds, due to the high frequency and variety of chromosome damage that occurs in solid tumors.

So where are we going with tumor markers? Hopefully, in the near future we'll have some new diagnostic-specific tumor substances. We also need markers that can describe tumor cell capability for proliferation, invasiveness, and metastasis. All of these factors are important in assessing the biological characteristics of a tumor, and provide an opportunity to develop accurate prognostic assessment.

(SLIDE)
New Therapies for Cancer

Immunomodulation with lymphokines

Immunotherapy with MABS

More aggressive chemotherapy

Oncogene/Suppressor gene control

Antisense oligonucleotides and RNA

Chemoprevention (vitamins, antiestrogens)

I think we can be encouraged about the progress that is being made with the development of new therapies such as oncogene/suppressor gene control with antisense oligonucleotides and new approaches such as chemoprevention. Can we identify premalignant lesions, such as Dr. Schwartz described with the polyp to carcinoma sequence, and then modulate that sequence to prevent cancer? Tamoxifen is being evaluated as a chemopreventive agent for breast cancer and synthetic retinoids are now being tested for the prevention of head and neck cancer and lung cancer.

(SLIDE)
Conclusions

1. Tumor marker monitoring can provide:
   - An assessment of response to therapy
   - Early detection of disease recurrence
2. When therapeutic options are available, this information can lead to enhanced patient care
3. More research should be directed to
   - The use of tumor marker panels
   - Consideration of the tumor marker half-life in determining the frequency of testing
   - Determining clinically significant changes in serial tumor marker values
   - Developing new tumor markers with greater clinical specificity and sensitivity

In conclusion, I hope that I have shown you that tumor marker monitoring can provide an accurate assessment of response to therapy and enable early detection of disease recurrence. When therapeutic options are available, tumor markers can help to enhance patient care. More research needs to be done to develop tumor marker panels. In order to improve the clinical accuracy of patient monitoring, more consideration must be

given to the tumor marker half-life and interpreting marker changes in terms of established criteria. Certainly we need to continue developing new tumor markers with greater clinical specificity and sensitivity, and, others that can address the biological properties of tumor cells.

Thank you. (*applause*)

SCHWARTZ: Thank you, Dr. Fritsche.

Suggested Reading

1.Sell, Stewart. Cancer markers of the 1990s. *Clin Lab Med* 1990; 10:1-37.

2.Virji M, Mercer D, Herberman R. Tumor markers in cancer diagnosis and prognosis. *CA* 1988; 38:104-136.

3.Herberman R & Mercer D, eds. *Immunodiagnosis of Cancer*, 2nd edition, Marcel Dekker (publishers), 1990.

4.Rose N, Friedman H, Fahey J, eds. *Manual of Clinical Laboratory Immunology*, 3rd edition. American Society of Microbiology, 1986.