Serum Tumor Markers for Patient Monitoring: A Case-Oriented Approach Illustrated with Carcinoembryonic Antigen

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The effectiveness of patient monitoring with serum tumor markers is improved when the patient's pretreatment baseline is established, regular serial testing is performed, and a clinically significant change of the marker is determined on the basis of objective criteria. Attention must be directed to (a) ensuring long-term assay precision, (b) timing specimen collection to avoid misinterpretation of paradoxical increases (induced by chemotherapy, surgery, or radiation), (c) noting changes in the production or clearance mechanisms of the marker, and (d) recognizing the variability of site-response in patients who have multiple locations of metastatic disease. Clinical decisions to alter therapy should not be based only on tumor marker measurements. In the absence of other clinical data, a tumor marker abnormality should be confirmed with serial samples collected at a time interval dictated by the half-life of the marker. Serial tumor marker testing can improve cancer patient care, especially when effective salvage therapies are available.

Indexing Terms: monitoring therapy, breast cancer, colorectal cancer

The objective of monitoring patients by using serum tumor markers is to provide data that assist in clinical decision making. Serial tumor marker data can reflect the patient's response to treatment and can provide an early signal of relapse or disease recurrence. To maximize the effectiveness of such testing, the clinician must: have a clear understanding of the production and clearance factors that affect the serum concentration of the marker; be aware of the accuracy and precision of the test method; and use objective criteria to define medically significant changes of serial tumor marker values.

Tumor marker production is a reflection of the synthesis and secretion capability of the tumor, the rate of cellular growth, necrosis, and, perhaps, programmed cell death (1, 2). It is now well established that tumors are composed of heterogeneous clones, each with differing capabilities for synthesis and secretion of a particular tumor marker. The marker production may be modulated by the host through endocrine, acute-phase, and immune responses. Thus, the steady-state concentration of the serum marker is the net result of production and various clearance mechanisms, including liver uptake, renal excretion, proteolysis, and protein binding.

Analytical considerations include assay specificity, sensitivity, and precision, especially on a long-term basis. The tumor marker laboratory must utilize rigorous quality-control measures to minimize the effect of lot-to-lot variation of assay reagents. Because most tumor marker test methods are immunoassays, consideration must be directed to the presence of interfering heterophile antibodies, e.g., human anti-mouse antibodies, which may cause either false-positive or false-negative test results (3).

The accuracy of data interpretation requires an assessment of intraindividual variation of the marker as established by the patient's baseline values. Values that exceed the baseline variation at either normal or above-normal levels may then be considered to be medically significant. But medically significant changes may be due to acute nonmalignant disease or altered clearance mechanisms. When these causes are ruled out, the tumor marker change may be considered an indication of a change in the status of the neoplastic disease. When monitoring patients undergoing therapy, the timing of specimen collection must be considered to avoid misinterpretation of therapy-induced changes.

Our knowledge of the clinical application of tumor markers for patient monitoring is primarily based on clinical experience and retrospective correlation of serial tumor marker values with the clinical course of the disease. Here, I present case histories to demonstrate the principles of serial monitoring. Patterns of carcinoembryonic antigen (CEA) concentrations in patients with colorectal and breast cancer are presented to demonstrate the usefulness and limitations of serum tumor markers for clinical management. CEA was selected as the model system because it most closely resembles the class of tumor-related glycoproteins and mucins currently under development as tumor markers. In addition, the general principles of patient monitoring demonstrated with CEA are applicable to serial measurements of chorionic gonadotropin (HCG) and a-fetoprotein (AFP) (germ cell tumors of the ovary and testis), prostate-specific antigen (PSA) (prostate cancer), and CA 125 (adenocarcinoma of the ovary).

Materials and Methods

Serum CEA was assayed with a solid-phase enzyme immunoassay employing polyclonal antisera (CEA-EIA; Abbott Diagnostics, N. Chicago, IL). Interassay precision (CV) was 10–12% at mean values between 3 and 5.

1 Nonstandard abbreviations: AFP, a-fetoprotein; CEA, carcinoembryonic antigen; SFU, 5-fluorouracil; HCG, human chorionic gonadotropin; and PSA, prostate-specific antigen.

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μg/L; 7–9% for mean values between 9 and 25 μg/L; and 9–11% for mean values ranging from 30 to 90 μg/L.

**Results**

**Colorectal Cancer**

Figure 1A shows the CEA pattern of a patient with colorectal cancer with liver metastasis who on the day of surgery had a high CEA value. After hepatic arterial infusion and chemotherapy, the patient had no evidence of disease by month 12. However, at month 23, a significant increase in serum CEA correlated with metastatic recurrence to the liver, which became clinically evident at month 27. After salvage surgery, the patient achieved a second remission, with the serial CEA values returning to normal baseline values.

Figure 1B shows the CEA pattern of another patient with colorectal cancer and liver metastasis who also had a high presurgical CEA value. The transient rise of the postsurgical CEA value, determined 1 week after abdominal perineal resection, was associated with surgical trauma and healing. Thus, it is recommended that the first postoperative CEA value be measured after 4–6 weeks, to allow for at least two or three CEA half-lives to pass (CEA half-life = 2 weeks). The increase in CEA seen at month 1 is consistent with the residual metastatic disease in the liver. Again, the high CEA value determined 2 days after chemotherapy is consistent with the necrotic release of CEA due to the cytotoxic therapy. The CEA value returned to normal at 8 months, at which time the patient had achieved only a partial remission. These two case histories demonstrate the importance of the proper timing of specimen collection for follow-up values during therapy. Trauma associated with surgery and cellular necrosis resulting from cytotoxic drugs can both cause transient increases of tumor markers, which can be erroneously reported as false-positive increases. Also, a normal tumor marker value observed after therapy may not indicate eradication of the tumor.

**Breast Cancer**

Figure 2 shows the CEA pattern of a breast cancer patient with skin metastasis who remained "stable" for 6 months while on vinblastine (Velban®) chemotherapy. During this stable response, the serum CEA showed significant increases, to 11.0 μg/L, at which time disease recurrence to skin was observed. After radiation therapy and chemotherapy with 5-fluorouracil (5FU), the patient achieved a complete remission and the CEA values returned to normal limits.

A breast cancer patient with bone metastasis undergoing tamoxifen therapy (Figure 3) had a significantly increased CEA value when she developed a malignant pleural effusion. The transient CEA increase observed between months 2 and 3 occurred while the patient was responding to chemotherapy. This paradoxical CEA increase was therapy-induced and reflected the sudden release of CEA due to cellular necrosis. The continual decrease of CEA to month 8 was consistent with a partial remission, as defined by a one-half volume reduction in the size of the chest wall lesion. The subsequent CEA increases were consistent with disease progression, first to bone and later to liver. Note that the rapid CEA increase during month 12 is associated with a significant increase in serum bilirubin and jaundice. Thus, the serum CEA increase reflected both increased production

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Fig. 1. Serum CEA patterns of two patients with colorectal cancer and liver metastasis which show the absence (A) and presence (B) of therapy-induced, transient CEA increases, demonstrating the significance of appropriate timing for specimen collection.

APR, abdominal perineal resection; HAI, hepatic arterial infusion; 5FU-IV, intravenous infusion of 5-fluorouracil; NED, no evidence of disease.

Fig. 2. Serum CEA pattern of a breast cancer patient who developed disease recurrence and responded to therapy.

NED, no evidence of disease.
from metastatic sites and decreased clearance of CEA by the liver.

Figure 4 also shows the CEA pattern of a breast cancer patient with bone metastasis. Her initial serum CEA value remained just slightly above normal at values between 7 and 10 μg/L during hormonal therapy with tamoxifen (months 2–14). She failed hormonal treatment and at month 14 developed disease progression in bone with no significant CEA increase. Hormonal therapy with megestrol acetate (Megace®; months 15–18) resulted in a twofold transient increase in serum CEA. She failed to respond to Megace and 5FU chemotherapy and died several months later. Thus, this patient maintained a constant production of CEA throughout the clinical course of her progressive disease. The transient CEA increase associated with Megace was treatment-induced and occurred as a result of a flare-type reaction commonly observed during the hormonal therapy of breast cancer patients (4).

Figure 5 shows the CEA pattern of a breast cancer patient who had metastatic disease in the chest wall and lung. The chest wall lesion showed an immediate response to chemotherapy. A partial remission was observed in the chest wall lesion at 6 months, but there was no change in the lung lesion. By month 11, the lung lesion showed a significant response, but the chest wall lesion had now progressed. A treatment change to tamoxifen resulted in a second partial remission of the chest wall lesion.

These CEA patterns from breast cancer patients show that increases in the serum tumor marker accurately reflect disease recurrence. Similarly, decreases in the marker after therapy can reflect the efficacy of treatment. Transient increases due to cytotoxic drugs and hormonal agents must be recognized as such, to prevent misinterpretation as false-positive changes. However, not all patients will benefit from tumor marker monitoring because some tumors will produce insignificant amounts of the marker.

Discussion

Serial changes in serum marker concentrations can provide an indication of therapeutic response in patients with neoplastic disease and give an early signal of disease recurrence in those patients who have previously responded to therapy. The CEA case studies presented in Figures 1–5 demonstrate the considerations necessary for the accurate interpretation of tumor marker data and are directly applicable to all other tumor markers as well. For example, the tumor-related mucins (CA 15-3, CA 549, M26, M29) have production and clearance characteristics similar to CEA; thus, they can be used in the same manner as CEA for monitoring breast and colorectal cancer (5).

Also, transient increases of HCG in gestational choriocarcinoma, and of AFP and HCG in testicular tumors, occur during the onset of chemotherapy. However, the duration of these transient increases is much shorter than that observed for CEA and the tumor-related mucins, reflecting the shorter half-lives of AFP and HCG, 5 and 1 days, respectively (6, 7). Discrepant responses of HCG and AFP during patient follow-up are reflective of the clonal nature of the tumors and the responsiveness of the cell clones to the chemotherapy (8). High AFP and HCG values that do not return to normal limits after chemotherapy are reflective of residual disease (9). For
patients in remission, clinically significant changes of the markers warrant therapeutic intervention, even in the absence of other clinical data confirming relapse (10).

PSA has significant value for assessing the efficacy of surgical and radiation therapy in patients with early-stage prostate cancer (11, 12). The extent to which the serum PSA decreases after radical prostatectomy has necessitated the development of PSA methods that have high anlyte sensitivity (13). These “ultrasensitive” PSA methods may provide an even earlier signal of disease recurrence after prostatectomy than is currently possible. In patients with advanced stages of prostate cancer, serial PSA measurements accurately reflect the clinical course of the disease (12).

Appropriate timing of blood collections for tumor marker assays is crucial to avoid erroneous interpretations of treatment-induced changes resulting from cytotoxicity and hormonal flare reactions. The frequency of serum testing should be based on the half-life of the marker, except, of course, when the marker baseline is being established. Clinically significant changes of the marker should be based on assessment of method precision and biological variation of the marker. In most cases, a change in the marker value of about ≥ ±25% is considered clinically significant (14, 15). However, in the absence of other confirmatory data, any abnormality of a tumor marker value should be confirmed with a second blood sample, collected at an appropriate time interval dictated by the half-life of the marker. When the serial trend confirms a clinically significant change, the patient’s work-up should include an assessment of nonneoplastic disease that might affect the marker clearance. However, even under ideal monitoring conditions, the tumor marker change may not be the earliest sign of change in the course of the disease; the marker production capability of the tumor must also be considered. When properly used, serial tumor marker testing can improve cancer patient care.

References