Perspectives on the Use of **Tumor Markers**

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Tumor markers are chemical or biologic characteristics that provide prognostic or predictive clues to tumor behavior. Prognostic markers offer prospective information about the natural history of tumor behavior, including information about chance of survival independent of therapy. Prognostic markers may identify patients who may not need or benefit from further therapy. Predictive markers provide information about the expected response to therapy, or toxicity associated with therapy. Predictive markers may influence the choice of therapy based on tumor and host profiles.

Today's challenge is that few prospective trials have formally tested the value of prognostic and predictive tumor markers. That situation, however, is changing as a number of ongoing and planned clinical trials are now focused on identifying tumor markers and validating their role as prognostic and predictive tools. In fact, the American Joint Committee on Cancer and the International Union Against Cancer established the following criteria to assess the value of candidate markers: determination of clinical importance, determination of independence, and determination of significance. In addition, the evolution of a "marker" to a "test" must also be feasible, reproducible, and widely available with appropriate quality control. Finally, these clinical trials must validate the use of tumor markers as being appropriate for broad-based conventional usage in clinical practice.

The studies of molecular and biochemical markers have also been challenged by the evolving field and methodology. Variation exists in the methods used to detect the marker (including reagents), the interpretation of the result (including controls), the reporting of the result (such as scoring and quality control), and the statistical interpretation (for example, cutoff points for positivity). While many obstacles must be overcome, the understanding and proper use of prognostic and predictive tumor markers can influence patient-care decisions.

Prognostic Markers

The most important prognostic marker for any tumor is the stage grouping using the tumor node metastasis (TNM) staging system. Based on the TNM variables, prognosis, independent of treatment effects, can be predicted. The importance of other histologic factors is tumor dependent, such as grade (validated in prostate cancer and sarcoma), vascular and lymphatic invasion (suggested for colorectal and pancreas cancers), and mitotic index. Patient-specific characteristics also play a role in determining prognosis, such as performance status and symptoms. Some molecular and biochemical markers are currently in use as prognostic markers, and many more are under investigation.

Serum tumor markers are validated prognostic indicators for some malignancies. Non-seminomatous germ cell tumors that secrete high concentrations of alpha-fetoprotein, beta human chorionic gonadotrophin, or lactate dehydrogenase have been shown to predict poor prognosis, despite the bulk of tumor.[1] Serum lactate dehydrogenase is also a prognostic marker for patients with non-Hodgkin's lymphoma, and is incorporated into the widely used International Prognostic Index to identify patients with an adverse prognosis.[2] Recent research suggests that the rate of rise of serum prostate specific antigen (PSA velocity) by more than 2.0 ng per milliliter during the year prior to the diagnosis of prostate cancer may portend a poor prognosis.[3] This factor may be an important indicator for identifying patients who may benefit from immediate surgery rather than "watchful waiting," or conversely identifying patients unlikely to benefit from aggressive surgery. The independence and clinical significance of this prognostic marker still needs to be established.

Predictive Markers

Estrogen and progesterone receptor determinations are established procedures in the routine management of patients with breast cancer. These markers predict the response to therapy with hormone receptor modulators. The method of determination of receptor status has evolved over the years, now predominantly utilizing immunohistochemical staining. Many scoring systems have been devised to distinguish tumors likely to respond to therapy from those not likely to respond. All of these variables contribute to the difficulty in comparing across studies.

The epidermal growth factor receptor (EGFR) is overexpressed in many cancers. The recombinant monoclonal antibody cetuximab binds and inhibits the activation of the receptor and its intracellular tyrosine kinase. Recent studies have demonstrated the efficacy of cetuximab in the treatment of refractory colorectal cancer.[4,5,6] All of these studies were conducted using patients with tumors that were shown to express the EGFR. There was no correlation of the intensity or percentage of cells staining for the EGFR and response to therapy. Furthermore, some reports have found a response to cetuximab in patients whose tumors do not demonstrate EGFR staining. The significance of the EGFR staining with current detection methods needs to be further evaluated as a predictive marker of response to therapy.

A member of the EGFR family, *erb*B-2 is overexpressed in about one-third of breast cancers through gene amplification. Overexpression of *erb*B-2 provides both prognostic and predictive information. This marker has been associated with reduced survival, but also indicates which tumors are likely to respond to the monoclonal antibody trastuzumab. These markers have played an important role in directing the treatment of breast cancer.

Gefitinib is a small molecule that also inhibits the activation of the EGFR and its intracellular tyrosine kinase. Gefitinib is approved for the treatment of non-small cell lung cancer, where it can produce a dramatic clinical response, although in only 10 percent of tumors. A recent study identified somatic mutations in the tyrosine kinase domain of the EGFR gene in eight of nine patients with gefitinib responsive tumors as compared with none of seven patients with gefitinib resistant tumors.[7] Furthermore, similar mutations were detected in two of 25 patients with non-small cell lung cancer who had not been exposed to gefitinib, approximating the incidence of responsiveness reported in clinical trials. Prospective validation of these findings may identify patients likely to respond to gefitinib.

Future Directions

As the genetic and molecular determinates that drive cancer are unraveled, and these findings are incorporated into new therapies, novel approaches to clinical trial design need to be explored. It is imperative that sample handling and methodology be standardized with accurate, reproducible assays. Interpretation and reporting of assay results need to be controlled and efficient. Appropriate candidate markers need to be explored in sufficiently powered studies.

One such study is the Eastern Cooperative Oncology Group coordinated GI Intergroup E5202 Stage II colon cancer trial. This study will stratify patients into high-risk and low-risk groups based on molecular profiles within the resected tumor. Colon tumors that demonstrate microsatellite instability or retention of the 18q allele have been shown in retrospective analysis to have a low risk of recurrence.[8] These patients will be assigned to the observation arm. Patients with colon tumors with high-risk features, particularly microsatellite stability with loss of the 18q allele, will be randomized to one of two different treatment arms of chemotherapy. The outcome of this study will clarify the role of these molecular markers as prognostic indicators.

Having a better understanding of the genetic and molecular biology of tumor growth will lead to improved prevention, diagnosis, treatment, and surveillance of cancer patients. With this understanding come complex assays, requiring interpretation, with associated variability. An overwhelming volume of information will become available with the standardization of microarray assays, which can identify many candidate markers within tumors. The challenge is to design meticulous clinical trials with clinically significant endpoints to sift through the plethora of information in a timely manner. Until these results are available, prior to pursuing marker evaluation, it is important for the physician and patient to discuss the technical limitations of these markers, the difference between prognostic and predictive markers, and the impact the result of the test will have on the treatment decision.

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