

ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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Predictive and Prognostic Markers in Cancer

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H&O Can you discuss the difference between a predictive marker and a prognostic marker?

DH A prognostic marker identifies outcome in patients, regardless of treatment, but is not necessarily only for untreated patients. Usually, these markers are thought to provide insight into risk of recurrence after surgery, but basically, prognostic factors are used to determine the “residual” risk after the preceding (or presumed applied) therapy, no matter what that therapy was.

A predictive marker is one that predicts whether or not the “next” therapy will work. Predictive and prognostic markers often get confused because many markers can be both predictive and prognostic. A marker can be an unfavorable prognostic factor but could predict favorably for response to therapy, or vice versa. Furthermore, it is possible that markers can be prognostically unfavorable, but predict favorably for one therapy and predict unfavorably for another therapy.

One of the problems with biomarkers is that, at times, an interesting biomarker is identified and then tested in studies of convenience, using specimens that happen to be available without clearly considering study design. Investigators should ask a question, then design their study with proper specimen selection, taking into account treatments and other factors, and then seeing if the biomarker answers that question, instead of running a study on available assays and samples, getting an answer, and then formulating the question.

H&O What is the ideal application of predictive and prognostic biomarkers?

DH The ideal application depends on the disease and the context in which the marker can be applied. One of the most useful new prognostic factors that has been developed in breast cancer in the last decade has been the 21 gene recurrence score (RS; *Oncotype DX*). Genomic Health, manufacturers of *Oncotype DX*, asked clinicians about the most important questions that arise in breast cancer treatment. The clinicians told them that approximately one-third of newly diagnosed breast cancer patients are node negative, estrogen receptor (ER)-positive without metastasis, and it is not clear if these patients should receive chemotherapy. The calculated absolute chance of benefit from chemotherapy, using online programs like *AdjuvantOnline*, in this patient population was only 2–3%. The 21 gene RS works with paraffin-embedded tissues and makes it possible to distinguish patients who are so unlikely to benefit from chemotherapy that the risks do not outweigh the benefits, from patients whose prognosis would warrant chemotherapy. The assay found that if a patient has a low recurrence score (node-negative, ER-positive) and receives only tamoxifen, she has a less than 10% chance of recurring over 10 years. Thus, treatment with only hormone therapy is recommended, because the benefits of chemotherapy do not outweigh the risks.

The 21 gene RS allows us to identify 50% of node-negative, ER-positive patients who fall into the low recurrence score group and 25% of patients who fall into the high recurrence score group, which then allows us to determine appropriate therapy. In the latter group, chemotherapy has proven to be worthwhile. However, this still leaves 25% of patients in the intermediate recurrence group, in which the response to chemotherapy is not high enough to suggest benefit but not low enough to eliminate it as a treatment option.

The North American Breast Cancer Group (NABCG; formerly the Breast Cancer Intergroup) recently completed accrual to the TailorX trial, led by the Eastern Cooperative Oncology Group (ECOG). TailorX is a large, prospective, randomized trial of node-negative ER-positive patients identified by 21 gene RS testing to be in the intermediate recurrence group. All of these patients received anti-estrogen therapy and were randomly assigned to chemotherapy or no chemotherapy. The hope with this trial is to determine the cut-off for chemotherapy benefit, and thus eliminate the intermediate category.

In addition to being prognostic, the 21 gene RS may also be predictive of benefit from chemotherapy. Twenty years ago, the Southwest Oncology Group (SWOG) conducted a trial within the Breast Cancer Intergroup in which postmenopausal women with ER-positive, node-positive breast cancer all received tamoxifen, and were randomly assigned to receive adjuvant cyclophosphamide, doxorubicin, and fluorouracil chemotherapy or not. Dr. Kathy Albain recently reported in the *Lancet* that, overall, chemotherapy modestly, but statistically significantly, improved disease-free and overall survival in this patient group. We applied the 21-gene RS test to tissues from these patients and found that, as expected, the patients with low RS who only received tamoxifen had a better prognosis than those with high RS, although as a group they still had a higher risk of recurrence than node-negative patients. Thus, the assay was prognostic. However, if chemotherapy works in this group, we would still use it (in contrast to node-negative patients with low RS), since enough patients are likely to benefit to outweigh the risks. More importantly, though, it appears that the assay is also predictive. In addition to having a better prognosis, patients with low RS did not seem to respond to chemotherapy; in other words, their prognosis was poor enough to justify chemotherapy, but it did not seem to work. In contrast, as RS got higher, not only did prognosis worsen, but the relative benefits of chemotherapy got larger.

H&O Can you explain validation for prognostic and predictive biomarkers?

DH The transition from an assay of interest to one that has clinical utility is based on 3 components. One component is analytic validity: the assay is stable, accurate for what is being measured, reproducible, and reliable, and works in the kinds of specimens that need to be tested. For example, the urokinase plasminogen activator/plasminogen activator inhibitor (uPA/PAI-1) assay, which is currently being used in Europe, does not work in paraffin-embedded tissue, which is the standard specimen used in the United States. This assay is highly analytically

validated in frozen tissue, but it is not used in the United States because it is not analytically valid in the kind of tissue (formalin-fixed, paraffin-embedded) that we commonly have available. The second component is clinical validity, which is whether the test identifies or predicts a patient's clinical status, meaning does it separate 2 populations with different clinical outcomes. The third, and key, component is clinical utility, which is the likelihood that the assay will significantly improve patient outcomes. If a marker has clinical utility, that means there are sufficient data to show it can be used to change practice. The best examples are ER status to predict if a patient will benefit from hormone therapy and HER2 status to predict whether a patient will benefit from anti-HER2 therapy. Outside of breast cancer, it is difficult to find a predictive or prognostic marker that is very well validated and has clinical utility; KRAS mutations for anti-EGFR antibody therapy comes the closest.

Dr. Richard Simon, Dr. Soonmyung Paik, and I published a paper in the *Journal of the National Cancer Institute* in 2009 addressing the topic of validation. In it we discussed hierarchies of study designs using archived specimens to evaluate the utility of prognostic/predictive biomarkers.

H&O How are biomarkers used in clinical trials, and are there any challenges to incorporating them into studies?

DH Biomarkers can be used in clinical trials to select people who may or may not be eligible for a study. There have been 5 major trials of adjuvant trastuzumab (Herceptin, Genentech) that included only patients who were HER2 positive; in this case, HER2 was used to select patients who were most likely to respond to trastuzumab treatment.

Biomarkers can also be utilized to monitor patients in a clinical study or can even be used as a study endpoint. The most definitive endpoint in oncology is survival. The problem with using survival as an endpoint is the length of time needed to measure it. Another issue with this endpoint is that patients who are dying of other causes as they age dilute survival. For these reasons, it is a difficult endpoint to measure and reach, at least in the adjuvant setting. The next most important endpoint is disease-free or progression-free survival. The third endpoint that is used in clinical trials is response. This is a much faster endpoint to achieve, and although it is less reliable, it is expedient. Similar to response, a biomarker can be used as an endpoint. If, in a study, an elevated level of a certain marker in the blood drops after treatment is given—and it is known that the reduction in the marker correlates strongly with response or prolonged progression-free,

disease-free, or overall survival—then it may be feasible to use that marker as a surrogate endpoint.

For example, circulating tumor cells (CTCs) appear to be an indication of drug response. There are many patients with metastatic breast cancer who do not have measurable disease, so it is not possible to measure drug response. However, if they enter a study with elevated CTCs, then a reduction in this marker might be interpreted similarly to a response in a measurable tumor. This has not been done yet, but I think we have enough evidence to suggest that we can use CTCs in this way. Certainly there are caveats to this approach, but nonetheless, these markers may provide an indication of whether or not the treatment is working.

H&O What are some recent studies of interest?

DH There are several interesting tumor marker–driven breast cancer trials currently ongoing in North America. Ki67, a marker of proliferation, provides another example of using a tumor marker as a surrogate endpoint. At the 2010 San Antonio Breast Cancer Symposium, Dr. Matthew Ellis presented an exciting follow-up study. In 2008, Dr. Ellis and colleagues looked at patients with S receptor–positive breast cancer who were given 4 months of endocrine therapy before surgery. They then used Ki 67, along with other characteristics of the residual tumor (such as tumor size, lymph node status, and ER status) to calculate a postoperative endocrine prognostic index (PEPI) score. This PEPI score predicted relapse-free survival in this study. Dr. Ellis and his colleagues in the American College of Surgeons Oncology Group are following up this observation in ongoing studies to further determine how best to use the PEPI score in ER-positive patients who undergo neoadjuvant endocrine therapy.

SWOG is currently conducting an ongoing trial evaluating CTCs (S0500, led by Dr. Jeffrey Smerage). In this study, metastatic breast cancer patients are being given 1 cycle of first-line chemotherapy, and if their CTC levels drop below 5 CTC/7.5 mL whole blood, it is assumed that treatment is working and it is therefore continued. If the CTC levels have not dropped, this suggests that the therapy is wrong for that patient. These patients are randomly assigned to switching therapy immediately or staying on the therapy they were originally assigned until there is classic evidence of progression. At present, we have 80 patients and are still accruing.

In another NABCg study led by SWOG, we are prospectively testing the clinical utility of using the 21 gene RS assay in node-positive patients. We are opening a new trial in women who are node-positive and ER-positive, with a low RS. These women will be given

anti-estrogen therapy and will be randomly assigned to chemotherapy or no chemotherapy to determine if our preliminary results, discussed above, can be validated. The standard of care for node-positive patients is chemotherapy, because they have a worse prognosis, but as discussed earlier, chemotherapy may not work in patients who are node-positive and ER-positive and have a low RS. This study will examine whether this group of patients is being overtreated just because they have a worse prognosis.

In addition to the circulating and tissue-based markers that have been discussed, there has been an increasing interest in inherited, germline genetic markers that may affect, and perhaps predict, susceptibility to a disease and, as more recently studied, effects from therapy. For example, it is now well established that women who harbor inherited abnormalities in BRCA1 and BRCA2 have a very high risk of developing new breast and ovarian cancers. These genes have clinical utility, since several studies have demonstrated that prophylactic surgery reduces the odds of developing, and dying from, new cancers.

The field of pharmacogenetics is less well established, but has lately gained great interest. Pharmacogenetics is the study of whether inherited, germline single nucleotide polymorphisms in genes responsible for drug metabolism, distribution, or activity influence patient outcomes. For example, individuals born with inactivating mutations of both alleles of CYP2D6 are unable to convert codeine to its active metabolite, morphine. Thus, these patients should receive an alternative analgesic. At present, there are no pharmacogenetic markers that have validated clinical utility for agents used to treat adult malignancies, but several studies are ongoing to address this important area.

Suggested Readings

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