Lab Tests for Chemotherapy Management
Chemotherapeutic drug management requires a multidisciplinary approach.

By Jill Hoffman

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Laboratory testing is changing the way patients undergoing chemotherapy are being treated and monitored. Gwen McMillin, PhD, medical director of Toxicology, co-director of Pharmacogenomics at ARUP Laboratories; and assistant professor of Pathology, University of Utah, Salt Lake City, believes chemotherapeutic drug management requires a multidisciplinary approach-from pharmacogenetic testing to clinical and radiographic assessments.

Pre-Treatment
Pre-therapeutic pharmacogenetics can help identify the best drug regimen for a particular tumor since tumors vary genetically.

Within pharmacogenetic testing, single-gene/protein tests such as HER2/neu protein have been used since 1998 to predict whether a breast cancer patient will respond to trastuzumab (marketed as Herceptin). Within the last few years, the KRAS test seeking gene mutations has helped predict whether colorectal cancer patients will be good candidates for drugs such as cetuximab and panitumumab, Dr. McMillin said.

Other tests being used in more niche populations and with less binary results are the CYP2D6 test for evaluating candidacy for tamoxifen. Thiopurine methyltransferase (TPMT) evaluates risk for toxicity from thiopurine drugs such as 6-mercaptopurine in children with acute lymphoblastic leukemia, and UGT1A1 predicts risk for toxicity from irinotecan.

With the exception of Herceptin, most single-gene/protein tests are not widely available. One reason relates to intellectual property. For example, access to TPMT genotyping is restricted because of an exclusive patent held by Prometheus Laboratories Inc.

Multi-gene expression arrays are another pre-therapeutic approach to create a profile for a tumor, predict patient prognosis and select treatment. Genomic Health Inc. offers Oncotype DX a 21-gene assay that predicts chemotherapy benefit and 10-year recurrence for women with early-stage breast cancer; Agendia puts out MammaPrint an in vitro diagnostic multivariate index assay using a bioinformatics algorithm for diagnosis, to predict spread and recurrence and select the best therapy.
The Trial Assigning Individualized Options for Treatment Rx sponsored by the National Cancer Institute is examining whether genes associated with recurrence in women with early-stage breast cancer can help assign patients to the most appropriate treatment. Doctors will use Oncotype DX to determine which women should receive adjuvant chemotherapy in addition to hormone therapy.

**Post-Therapy**

While pre-therapeutic tests help evaluate a patient's predicted response, they aren't a perfect system, Dr. McMillin said. Improvements could come from establishing better correlations between drug response, toxicity and drug concentrations circulating in the body. Examining metabolite concentrations (as most cancer drugs have to be converted metabolically to active drugs-metabolites) after a patient has started receiving treatment can guide future therapy.

And, because the body eliminates metabolites at a unique rate that cannot always be predicted, the ratio of the parent drug to the metabolite or metabolite pairs could be revealing.

Busulfan is routinely used for this purpose in patients undergoing bone marrow transplants. In the common Q6 chemotherapy paradigm, a patient receives 16 doses six hours apart, so examining how the patient is handling the drug helps refine dosing and reduce toxicity risk, Dr. McMillin said. "It's one drug for which the package labeling actually recommends doing this," she added. No commercial metabolite concentration tests are available, so labs must develop their own tests or partner with others that have them.

Dr. McMillin believes there is not enough routine testing of cancer drugs in patients, but methotrexate is one exception. An antimetabolite/antifolate drug to treat cancer and autoimmune diseases, it is often monitored because there's an antidote--Leucovorin--if a patient gets too much.

Beyond these lab tests, Dr. McMillin suggests that biomarkers of response and clinical and radiographic assessments are important for treatment follow-up to evaluate cell proliferation processes, tumor size and whether patients' symptoms have subsided.

Dr. McMillin hopes the FDA and organizations such as the American Society of Clinical Oncology will consider the value of pre- and post-therapeutic tests when evaluating new or existing therapeutic drugs known to exhibit toxicity or poor response rates.

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