CUSTOM
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TEST YOUR TUMOR. WHAT WORKS AND WHAT DOESN'T.
In 1954, two New York Medical College scientists, Maurice Black, MD, and Francis Speer, MD, published a paper in the Journal of the National Cancer Institute (JNCI) that challenged the concept of one-size-fits-all chemotherapy. They described a novel test, or assay, that exposed a piece of a cancer patient's tumor to chemotherapy drugs in a test tube to see which ones inhibited growth and which did not. The maverick

BY CHRISTINE HARAN
researchers then compared the test-tube response with the effect on the tumors in patients’ bodies.

The concept was revolutionary: Tumor assays could theoretically help doctors choose the most effective chemotherapy agents, sparing their patients toxicity from drugs that provide no benefit. But the test’s predictive accuracy rate was poor, the researchers reported, so few oncologists took note of the technique. Moreover, in the ’50s, there were only about two or three chemotherapy drugs from which to choose.

Twenty-four years later, the medical community became interested when an apparent breakthrough took place. A June 1978 paper by Sydney Salmon, MD, and Anne Hamburger, PhD, et al, published in the prestigious New England Journal of Medicine (NEJM), introduced a promising new assay. In this assay, rather than a test on a slice of tumor, patients’ cancer cells were selectively grown in a culture before being exposed to chemotherapy drugs. The National Cancer Institute (NCI) and others poured money into study of the assay, and laboratories nationwide began advertising it for clinical use.

But the excitement fizzled after a 1983 NEJM editorial and accompanying letter concluded that it was premature to use the assay in the routine selection of drugs. Scientists could only get the cultured cancer cells to grow about 30 percent of the time, and only 8 percent of cells that did grow demonstrated sensitivity. Furthermore, the data showing a correlation between the test results and patient response were deemed unreliable. The setback seemed to mark the end of an era. In the words of Larry Weisenthal MD, PhD, founder of the Weisenthal Cancer Group, a private cancer drug testing laboratory in Huntington Beach, California, “It sounded the death knell of this assay and the take-home message was, ‘Nothing will work.’”

Today, the need for accurate tumor assays would seem more pressing than ever. There are more than 30 government-approved chemotherapy drugs, numerous regimens involving combinations of those agents and more drugs in the pipeline. “It has not been established that there is one form and one form alone of chemotherapy that has to be used,” Dr. Weisenthal says. “If you’ve got technology that can discriminate between the good and bad choices, let’s use it.”

Weisenthal is one of several researchers and oncologists who have continued to refine assay techniques. “Since the mid-’80s, with no support from their academic institutions, there have been people who have stubbornly kept at it,” he says. “This is not a situation where you have greedy entrepreneurs but people who felt they had something that would work.”

Many members of the medical mainstream still believe the technology doesn’t work well enough and that it could even be dangerous to rely on the tests. But a growing number of oncologists assert that the technology, sometimes called “Designer Chemo,” is useful as part of the profile of an individual tumor. They say people with cancer have a right to know the technique is available to them. A handful go so far
as to argue that assays are already saving lives.

TESTING FOR DRUG RESISTANCE

There are two kinds of tumor assays: those that pinpoint ineffective drugs (chemoresistance) and those that select drugs likely to work (chemosensitivity). Drug resistance assays are generally considered by the medical establishment to be the most credible type of assay. In 1990, Weisenthal and David Kern, PhD, published a paper in the *JNCI* on the Extreme Drug Resistance (EDR) assay, which exposes a tumor cell culture to high concentrations of drugs for long exposure times. They reported that the EDR identified extreme drug resistance with more than 99 percent accuracy.

Assays are better “at ruling out agents than selecting agents,” says Kern, a consultant and scientific adviser at Impath, a cancer laboratory based in New York City, which began offering a drug resistance assay in June. Kern emphasizes that eliminating one drug does not necessarily mean another drug that did not show resistance will work. “We’re talking about a small step,” he says. “It’s one piece of information—you use it with all the other clinical data and what you know about the individual patient—and make a rational decision. That’s the responsible way to use these tests.”

Oncotech, a molecular oncology lab in Irvine, California, founded by Weisenthal and Robert Nagourney, MD, has been offering the EDR assay commercially since 1988. Oncotech currently tests about 10,000 tumor specimens a year, sent from more than 800 hospitals nationwide. The company is respected by the medical community, in part, because of its commitment to clinical trials. “Oncotech has been very forthright in its desire to do studies,” says Maurie Markman, MD, chairman of the department of hematology and medical oncology at the Cleveland Clinic Cancer Center in Ohio. Oncotech is currently testing the EDR assay in three mid-sized (50 to 100 patients) prospective clinical trials and one Phase III trial in Europe.

Last May, Oncotech medical director and senior vice president John Fruehaufer, MD, PhD, presented a paper at the American Society of Clinical Oncologists conference on a prospective trial of 102 breast cancer patients. The updated results show that after 50 months, the survival rate was 80 percent for those who received drugs to which they had shown low resistance, versus 45 percent for patients who had intermediate or extreme resistance to even one of their treatment drugs. Oncotech’s first prospective ovarian cancer trial was published in *The Cancer Journal from Scientific American* in the same month: The study of 66 women showed that EDR-directed treatment spared toxicity and cost without affecting survival.

“The current evidence published in more than 60 independent papers clearly supports the view that in-vitro drug response testing can identify drugs that won’t be effective prior to their administration,” Dr. Fruehaufer says. “There are many different new agents available, and selection can be significantly enhanced through the elimination of inactive agents.”

Now in private practice, Weisenthal tests to select drugs using three types of assays. While Oncotech tests each specimen with five to eight single agents, Weisenthal uses 18 to 25 drugs, evaluating some in combinations.

Weisenthal recommends sensitivity testing for both untreated and relapsed patients. Richard Nalick, MD, is a Los Angeles-based gynecological-oncologist who bases all his ovarian cancer patients’ treatment on the drug combination Weisenthal’s assays indicate will work. Dr. Nalick stresses that standard drugs are used and that oncologists are “programmed” to think the current gold standard for ovarian cancer—Taxol (paclitaxel) and carboplatin (Paraplatin)—is the only combination that has been proven.

One of Nalick’s patients, Harriet Silverman, 64, of Oxnard, California, was diagnosed with Stage IIIIC ovarian cancer in May 1993. Silverman, now in remission, is currently on a gemcitabine (Gemzar)/cisplatin (Platino) combination. She received no benefit from Taxol, which she took between her first and second surgeries. “I wasted a year of my life,” Silverman says. “I was tested for Taxol afterwards and I came out zero. The assay to me is a lifetime.”

Dr. Nagourney, also now in private practice, has achieved some fame as the medical oncologist for the late *Harper’s Bazaar* editor-in-chief Liz Tilberis. He tested Tilberis, who died last spring after responding to drug therapy for months, at Rational Therapeutics, his drug testing and treatment institute in Long Beach, California. According to Nagourney, Tilberis—who coined the phrase “Designer Chemo” and promoted the assays in her magazine—had trouble withstanding even mild treatment regimens after the bone marrow transplant she had received before seeing him.

Like Weisenthal, Nagourney looks for drugs that induce cancer cell death rather than inhibit their growth. His assays have occasionally led him to recommend unconventional chemotherapy regimens for patients, some of whom have had remarkable success with the treatment.

Ovarian cancer survivor Josephine Hanson was, in Nagourney’s words, “given up for dead” by City of Hope Medical Center in Duarte, California when she first went to see him. Hanson had heard Nagourney speak and had told herself she’d see him if her treatment failed again. The 64-year-old, diagnosed with Stage IV disease in 1995, had been through three surgeries and several rounds of chemotherapy, including a bone marrow transplant. Nagourney performed an assay and put Hanson on a gemcitabine/cisplatin combination, even though she had failed gemcitabine as a single agent. Within eight weeks, Hanson’s CAT scans were almost normal, and as of this writing, she appears to be in complete remission, according to Nagourney. “Gemcitabine (alone) did me no good whatsoever,” Hanson says, adding that if she had an assay performed earlier, she “would have probably been saved another tumor…and a lot of discomfort.”

Not all cancer patients can take advantage of the tests, however. Both resistance and sensitivity assays must be performed on live tumor specimens, and not all tumors are oper-
able, or contain enough cancerous tissue or fluid to provide a specimen. According to Kern, assays tend to be performed more often for ovarian than breast cancer patients because almost all ovarian cancer is treated with chemotherapy and diagnosed at advanced stages when tumors are large. Still, even if the tissue gets to the lab, there’s a 10 to 15 percent chance the cells will not grow, leaving the specimen useless.

SKEPTICISM

Despite the success stories, there is less documentation to support sensitivity testing than resistance testing: A 1993 review in the Principles & Practice of Oncology concluded that chemosensitivity assays could not be expected to select drugs with more than 72 percent accuracy. “It’s questionable as to whether you can select active drugs,” says Impath’s Kern, adding that a test tube is a far simpler environment than the human body.

“Drug sensitivity testing has not been demonstrated to be sufficiently reliable for standard patient care,” agrees Daniel F. Hayes, MD, clinical director of the breast cancer program at the Lombardi Cancer Center at Georgetown University in Washington, DC. Though he acknowledges that the EDR appears to be a sound test, Dr. Hayes does not recommend chemosensitivity or chemoresistance testing to his patients.

The Cleveland Clinic’s Dr. Markman is strongly opposed to the use of first-line regimens that are not considered the standard of care: “Denying women proven therapy based on something they have done in a lab [that] we have no evidence for is outrageous,” he says. David Spriggs, MD, chief of the developmental chemotherapy service at Memorial Sloan-Kettering Cancer Center in New York City, occasionally sends tumor specimens from relapsed ovarian cancer patients to Oncotech. He says, however, that Nagourney has sometimes “recommended a three-drug treatment with no published literature (to back it up). I consider that to be unhelpful and potentially dangerous.” Dr. Spriggs adds that Taxol should always be given as first-line ovarian cancer treatment.

Markman does not believe in assays in choosing therapy for relapsed cancer either. “When used (after the first recurrence), I don’t think it’s any better than my empiric judgment, but I don’t think the patient has been harmed.” Spriggs, however, says the assays can be of use after the first or second recurrence. “It’s only with recurrence that there are enough medicines that [assays are] actually helpful,” he says. Spriggs is currently setting up an EDR trial for women with recurrent ovarian cancer with David Gershenson, MD, of University of Texas MD Anderson Cancer Center in Houston.

CLINICAL TRIALS

Critics and proponents alike tend to agree on the need for large, controlled, randomized clinical trials that would compare survival rates. An article published in the May 1999 Journal of Clinical Oncology came to the same conclusion after reviewing 12 prospective studies that examined the benefit of chemotherapy selected by drug sensitivity testing. The authors determined that response rates seemed better with chemotherapy regimens selected on the basis of the assay than those chosen without the assay but said impact on survival had not been adequately addressed by the studies.

Why hasn’t there been large-scale trials? Many researchers say they’ve tried to complete them for years, to no avail. Nagourney has submitted more than a dozen grant applications to major peer-reviewed funding agencies, such as NCI, and cooperative groups, such as the Gynecologic Oncology Group (GOG). “If you dusted the applications for fingerprints, you wouldn’t find any,” he says. “They have consistently turned this down.”

Weisenthal says he got two large prospective trials off the ground in the late ‘80s but couldn’t recruit enough patients. He has since given up on organizing trials. “I [thought it would be] better to start doing it,” he says. “At a certain point, [the tests] just can’t be ignored.”

In 1993, the GOG did launch an EDR study with Oncotech for newly diagnosed ovarian cancer patients, but it was closed early because not enough people were enrolled. Kern set up a drug resistance trial for ovarian cancer with Kaiser Permanente that same year, but it ended in 1995 after the NEJM published a paper indicating Taxol should be first-line therapy for all ovarian cancer patients. According to Kern, Kaiser’s lawyers “feared liability.

Many oncologists attribute the lackluster response to the history of the assays. “They’re swimming upstream because the early technologies were so poor; people got turned off,” Hayes says. “Their reputation has preceded them.”

Robert M. Hoffman, PhD, president of AntiCancer, a biotechnology company in San Diego that licenses its drug sensitivity test in Japan, says drug companies have no interest in funding assay trials. Kern likewise notes that enrolling patients is difficult when there are competing trials using exciting new drugs. “This is not a new therapy,” he says. “It’s just a lab test. It doesn’t cure people; it just predicts. A trial is not that appealing.”

INFORMED CHOICES

Although a large-scale trial might never get started, tumor assays nonetheless seem to be drifting toward the mainstream. Gail Hayward, president of the Pompano Beach, Florida–based National Ovarian Cancer Coalition (NOCC), is an advocate of the technique. Hayward—who has been on chemotherapy for nine and a half years—had assays performed at the Weisenthal Cancer Group in 1994. Although she didn’t use the assay results right away, she is now responding well to the recommended drugs. “[It’s about] having the right to make informed, educated choices” she says. “It’s one more ticking-off mark to put on your list of to-dos for treatment.”

Michael Method, MD, MPH, chair of the medical advisory board of NOCC, also sees a place in treatment for tumor assays. “In general, the thought and feeling among most GYN oncologists is that there is a role for the technology,” he says. “That role is being developed, and the future holds promise for individualized chemotherapy.”

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