PERSONALIZED MEDICINE

What is Missing?

by JENNIFER LEVIN CARTER, MD, MPH with JILLIAN LOKERE

Jennifer Levin Carter

Cancer treatment has changed dramatically over the last few years. It is now not only possible, but also often important to go beyond classifying tumours based on where they occur in the body. In fact, two patients with cancer of the same organ of origin may well have two very different cancers that can require different treatment strategies. Decades of painstaking research have demonstrated that each tumour has a unique set of genetic aberrations and molecular changes. Some of these genetic and molecular characteristics have been termed biomarkers since they can mark how well a tumour will respond to certain treatments or how quickly the disease will progress.

The goal of biomarker research in oncology is to personalize cancer treatment based on individual tumour characteristics. In the ideal scenario, each tumour is tested to identify its unique biomarker profile and that information helps to inform decisions about prognosis and treatment. In some circumstances, treatments may be selected more effectively based on the biomarker profile of a patient's tumour. Drugs that are not likely to work or are not necessary can be avoided, thus saving the significant costs, both financial and personal, of needless therapy.

This is the future of cancer care, but we are not there yet. What is missing? To answer this question, it is instructive to review the progress that has been made. The journey from the general (all breast cancers are the same) to the specific (breast cancers are of several types) to the near-personalized (your breast tumour has biomarkers that indicate it will respond well to a particular treatment strategy) began in the 1970s with the discovery of the first biomarker: the estrogen receptor (ER).

The Biomarker Revolution

In 1971, Elwood V. Jensen at the University of Chicago showed that breast tumours rich in ERs were more likely than ER-poor tumours to respond to treatment that would reduce the amount of circulating estrogen in the body.[1] When the anti-estrogen compound tamoxifen[2,3] was discovered as part of a fertility control program, its potential for the treatment of breast cancer became the subject of much research. By 1973, tamoxifen was known to interfere with estrogen's ability to stimulate the growth of breast cancer cells and was recognized as an effective treatment approach for breast cancer rich in ERs ("ER-positive" cancer).[4]

The real breakthrough in biomarker discovery, however, came a few years later. Before the mid-1970s, researchers knew that certain genes, termed "oncogenes", seemed to be responsible for the unchecked growth and division characteristic of cancer cells. At the time, it was widely believed that oncogenes were viral in origin, not human, and that the cause of all cancer was infection of human cells by viruses containing these viral oncogenes. In 1976, J. Michael Bishop and Harold E. Varmus of the University of California, San Francisco demonstrated that oncogenes are human in origin and can be found in normal human cells. For this revolutionary discovery, Bishop and Varmus were awarded the Nobel Prize in Physiology or Medicine in 1989.[5] Armed with a completely new model for understanding cancer, researchers started to study how normal human genes could change to become cancer-causing oncogenes. The race to uncover new oncogenes was on.

One of those newly discovered oncogenes was HER2/neu. Studies by Genentech scientists in the early 1980s demonstrated that, in normal human cells, the HER2/neu gene produces a protein that regulates cell growth. In 1987, Dennis Slamon at the University of California, Los Angeles and colleagues from the University of Texas studied breast tumour samples and found that cancer cells from 25 per cent of the patients contained many more copies of the gene than did normal breast tissue cells. This resulted in abnormally high levels of the HER2/neu protein ("HER2/neu overexpression").

Most importantly, they found that patients whose tumours had higher levels of HER2/neu protein had a shorter time to relapse and a shorter overall survival time. In sum, the work showed that a high level of HER2/neu in a patient's tumour was a reliable biomarker for aggressive tumour growth and a worse prognosis.[6]

In response to this discovery, researchers from Genentech developed a drug to bind to excessive HER2/neu on breast tumour cells, slowing their growth and triggering the patient's immune system to destroy them. By May 1998, the resulting molecularly targeted agent, Herceptin (trastuzumab), had been shown to increase response rates by about 50 per cent and improve time to disease progression by about 60 per cent when used with chemotherapy for women with metastatic breast cancer.[7] Herceptin was approved by the United States Food and Drug Administration (FDA) later that year, followed by approval by Health Canada in 1999.

During the same time period that HER2/neu was discovered and targeted through the development of Herceptin, another well-known cancer biomarker was exploited for rational drug design: the Philadelphia chromosome. This genetic mutation results from a translocation, or break-and-swap, that results in part of human chromosome 22 being joined to chromosome 9.[8] Termed BCR-ABL, this new gene produces a protein that causes uncontrolled white blood cell growth and division in Chronic Myelogenous Leukemia (CML). Researchers at Novartis (then Ciba-Geigy) developed an inhibitor of the BCR-ABL protein, imatinib (Gleevec). By 1999, early clinical trials of Gleevec demonstrated remarkable response rates of greater than 90 per cent.[9] In 2001, Gleevec was approved in the United States and Canada for Philadelphia (Ph) chromosome-positive CML.

The success of Herceptin and Gleevec paved the way for additional important advances in the field of molecularly targeted therapy. Since 2001, the number of known biomarkers and targeted therapeutics has grown exponentially. We now know that a single biomarker is not always confined to one type of cancer. The Epidermal Growth Factor Receptor (EGFR) is one example. EGFR is a protein that can be overexpressed or abnormally active in the tumour cells from several cancer types, including lung, colon, head and neck, pancreatic, and brain. EGFR is the target of more than one drug: gefitinib (Iressa), erlotinib (Tarceva), cetuximab (Erbitux), Vectibix (panitumumab), and lapatinib (Tykerb).[10] Such medications are typically tested in and approved for use in a single type of cancer first, then further trials are conducted in other types of cancer that express the appropriate biomarker. This is the case for Herceptin, a drug originally tested and approved for metastatic breast cancer expressing the biomarker Her2/neu. In late 2010, Herceptin was approved by the FDA and Health Canada for use in HER2/neu-positive metastatic stomach cancer.[11]

Advances in oncology research have demonstrated that biomarkers are not limited to a paradigm of "one biomarker—one targeted agent." In fact, the biomarkers present or absent on a patient's tumour make up a unique molecular profile that can, in some cases, help physicians predict the patient's response to chemotherapy, targeted therapy, or both. One good example are the multi-gene assays, which are laboratory tests that check a tumour sample for multiple biomarkers at the same time. Such multi-targeted assays are an important area of research. Some examples include Mammostrat and MammaPrint for breast cancer, and Oncotype Dx for breast and colon cancers. Clinical studies have shown that these panels can, for certain cancers, divide patients into groups according to their risk of recurrence. Those in the high-risk group have been shown to benefit from an aggressive course of chemotherapy after surgery, while patients in the low-risk group do not appear to benefit.[12,13] Another example is the biomarker KRAS. A 2009 study found that patients with metastatic colorectal cancer whose tumours had a normal KRAS gene were more likely to respond to a combination of chemotherapy and Erbitux than those whose tumours had a specific mutated version of the KRAS gene.[14]

The strategic use of tumour biomarker profiling can help spare patients from the lost time and potential side effects that come from trying a medication that is unlikely to be effective. Further, tumour biomarker profiling can produce significant savings on a national scale. In the case of KRAS testing, a U.S. pharmacoeconomic study found that upfront KRAS testing of tumours from patients with colorectal cancer would cost $13 million annually but would result in a net savings of $740 million, a savings realized through the avoidance of Erbitux treatment in those patients very unlikely to respond.[15] Clearly, moving toward large-scale biomarker testing makes financial sense for large-scale payers; however, it is important to keep in mind that the benefits—to patients and to payers—cannot be realized unless a testing program is under strict quality control and produces consistently accurate results. These issues cannot be taken for granted, as made clear by a 2009 study from the University of California, San Francisco that found approximately 20 per cent of HER2 tests conducted today are inaccurate.[16] The Commission of Inquiry on Hormone Receptor Testing in Newfoundland, released in 2009, revealed that 383 breast cancer patients of 1,013 tested between 1997 and 2005 had inaccurate ER/PR results, which in many cases led to the omission of appropriate hormone therapy.[17] This strongly highlights the need for strict quality control when national programs for biomarker testing are undertaken.

From Targeted Therapeutics to Personalized Medicine

With all of the advances in molecular medicine, it is frustrating to realize that the goal of personalized treatment has still not been attained. The average five-year survival rate for cancer patients in Canada is still just 62 per cent, and about a quarter of cancer types have five-year survival rates under 25 per cent.[18] This is the reality even though there are more than a hundred approved cancer drugs in Canada, including 24 molecularly targeted agents. Is the problem that the available drugs are not effective? Certainly continued development of efficacious drugs is needed. Tumours can develop resistance to both standard chemotherapy and targeted agents over time. Yet, a major part of the problem in most countries is the unacceptably long lag time between the attainment of knowledge by the research community and the integration of that knowledge into the standard of care. On average, it takes 17 years for new treatment strategies to become part of published guidelines.[19]

The reasons for the lag between the research and bedside are complex. Cancer treatment is one of the fastest moving fields in medicine. The explosion of research is overwhelming, and it is challenging even for those who craft the guidelines to keep current. In addition, key opinion leaders do not always agree about whether or not a new medication or treatment strategy has enough data to support its incorporation into the guidelines. Once new research appears in the guidelines, there is a further lag as clinicians incorporate the updated guidelines into practice. A recently published U.S. National Cancer Institute (NCI) Office of Education and Special Initiatives survey of 2,864 oncology practitioners in all types of practice settings found that only 33 per cent indicated that they had adequate time to access best-practice information.[20] Regardless of the reasons, the current model for cancer care remains, in some ways, stuck in the past.

For example, the Tumor-Node-Metastasis (TNM) staging system was devised in the 1940s.[21] Under this system, all tumours of the same stage and organ of origin are given a similar prognosis and are approached with a similar treatment strategy. Yet, one tumour may respond well to a particular chemotherapy or targeted agent, while another "similar" tumour will continue to grow and progress. Biomarker tools, where they have been developed, may offer a better assessment of risk than does the TNM system. For example, many patients in the clinical trials of multi-gene assays were labeled as high risk by the TNM system but low risk by the assay. These patients would have almost certainly received chemotherapy that followed the standard of care, yet the multi-gene assay revealed that they did not require such an aggressive course of treatment.[22] Although these data have been published for four years, multi-gene assays are still not routinely used in the management of breast cancer in Canada, and their cost is rarely covered by the provincial health care plans. In practice, this means that Canadian breast cancer patients will receive unnecessary chemotherapy.[23,24] Clearly, something must be done about the lag between the advancement of knowledge and its implementation in the clinic.

As the pace of research and development in oncology treatment continues to accelerate, bridging strategies will become increasingly necessary to make personalized cancer treatment a reality. Busy clinicians will need to find time-sparing and cost-effective ways to bring individualized treatment strategies to their patients. Patients will want a way to play an active role in their disease management in a manner that goes beyond internet searching and recommendations from friends or family. Payers and drug developers have a stake in ensuring that health-care dollars are spent on therapies that have the highest likelihood of producing a disease response. These goals are attainable—if knowledge from research can be quickly moved into the mainstream cancer community. The age of personalized medicine is, indeed, upon us, and it is up to us to seize that opportunity.

Jennifer Levin Carter, MD, MPH, is the Founder, President and Chief Medical Officer of N-of-One Therapeutics, Inc. (www.n-of-one.com). Dr. Carter is a physician, entrepreneur, and former healthcare analyst in bio- and medical technology. She graduated with distinction in Molecular Biophysics and Biochemistry from Yale University. She received an MD from Harvard Medical School and a Masters of Public Health from The Harvard School of Public Health.

Jillian Lokere is a freelance science and medical writer.

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