New yardstick could speed access to cancer drugs for surgery

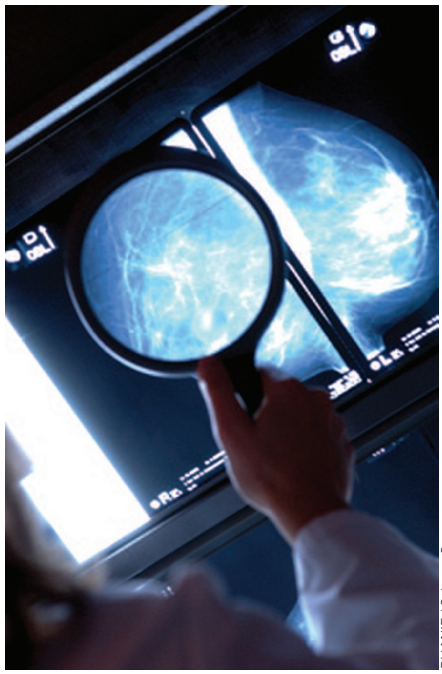
More and more, the first stop for a woman newly diagnosed with breast cancer is the chemotherapy ward rather than the operating room. That's because doctors have shifted toward offering 'neoadjuvant' therapy, treatment given prior to surgery to reverse or stabilize tumor growth. After this pretreatment, increasingly there are cases in which, during surgery, the removed breast tissue and surrounding lymph nodes show no signs of cancer, a situation known as 'pathological complete response', or pCR. To keep pace with this trend, the US Food and Drug Administration (FDA) is moving toward issuing final guidance on the use of pCR as a clinical trial endpoint for accelerated approval of drugs given ahead of breast cancer surgery to reduce—or obliterate—tumors.

The move, which is expected to come by the end of 2013 and perhaps as early as this summer, would mark the first time pCR, rather than overall survival or disease-free survival, could be used as an endpoint for regulatory approval. And the change, the FDA says, would mean that positive results from shorter, smaller studies could get promising breast cancer drugs to market sooner than is currently possible.

"Older models require studies that are very lengthy and resource intensive," says Tatiana Prowell, an oncologist at the Johns Hopkins Sidney Kimmel Comprehensive Cancer Center in Baltimore and a medical officer in the FDA's Breast Oncology Group in Silver Spring, Maryland. "This, I think, would make the process more nimble, in that fewer patients are needed and you'll get that proximal endpoint very quickly."

Traditionally, most new cancer drugs are first put to the test in patients with advanced forms of cancer who have resisted other treatments and often have tumors that have spread throughout the body. Such trials typically look at the survival statistics of these patients over a time frame of at least a couple of years. But recently, more drugs—both those already approved as post-surgery adjuvants and investigational drugs in trials—have been studied as neoadjuvants, testing the idea that some therapeutics might actually work better, or differently, in newly diagnosed patients whose cancer hasn't spread. In these studies, pCR, which can be determined immediately after a woman has surgery and within months of a study's start, often acts as an early marker of survival benefit.

"There's evidence that pCR is associated with a very favorable long-term outcome," says oncologist Eric Winer of the Dana-Farber Cancer Institute in Boston. "If you compare patients who have a pCR to those who don't, the patients with pCR do much better." For example, studies that added Herceptin (trastuzumab), an antibody drug from South San Francisco's Genentech, on top of chemotherapy in a neoadjuvant setting have found that the preoperative treatment led to rates of total pCR as high as 40%, with concurrent improvements in survival (*Lancet* **375**, 377–384, 2010; *J. Clin. Oncol.* **29**, 3351–3357, 2011). Australian regulators approved Herceptin as a neoadjuvant in 2012. As of yet, no drugs have been approved as neoadjuvants in the US, although many cancer drugs are given off label as such. The FDA is considering giving the go-ahead for this use, however. In May 2012, the agency released draft guidance on the use of pCR as a regulatory endpoint; continued approval of the neoadjuvants approved in this pathway would still be contingent upon further trials that included survival data, according to the proposal.



PHANIE / Science Source

Means to an endpoint: Experts debate pCR.

Faster by design

For researchers and companies involved in clinical trials, this new approval process will probably change study designs. Whereas some companies might simply add pCR as an early measurement of benefit into their existing trials aimed at gauging survival benefit, others would be likely to design small initial studies aimed at pCR endpoints before convening larger, longer studies separately.

"You could have results in six months, and using a smaller study," says pathologist William Symmans of the MD Anderson Cancer Center in Houston. "And you'd be bringing agents into this newly diagnosed population."

But there will be no one-size-fits-all approach to approval—nor a specific percentage of patients achieving pCR that the FDA would like to see to grant approval, according to Prowell. Instead, the agency will manage decisions on a case-by-case basis.

Although the new rules would change some breast cancer studies, pCR is difficult to assess in cancers that are diffuse or more aggressive, Symmans says, so the move is not likely to lead to changes to other malignancies in the very near future. For now, he says, the data are sufficient to use pCR as an endpoint in only HER2-negative and triple-negative breast cancers. But researchers continue to study the potential of pCR as a marker of survival in other types of breast cancer and in colorectal and esophageal cancers, among others.

Researchers and the FDA both stress that before the final guidance is issued, an agreement must be reached on exact, standardized methods for how tissue samples are collected and analyzed for pCR. As press time, these issues of standardization were scheduled to be discussed at a public workshop at the FDA on 22 March and at a scientific panel convening 8 April at the annual meeting of the American Association for Cancer Research in Washington, DC, after which the FDA will move forward on its final guidance.

If the shift to pCR as a regulatory endpoint occurs, Symmans expects it would mean an increased involvement of pathologists—who analyze tissue specimens for evidence of cancer—in clinical trials. "I think there are going to be much more sophisticated, more data-driven refinements to the pCR endpoint in years to come," he says. "But there's enough data already for the FDA to get going with using this as an endpoint, and I think it's going to be good for patients, and it's going to be good for drug development, and it's going to be good for clinical trials."

Sarah CP Williams