Circulating Tumor DNA — Ready for Prime Time?
Marc Lippman, M.D., and C. Kent Osborne, M.D.

Multiple aspects of the management of metastatic breast cancer need improvement. Patients are anxious about their risk of recurrence and are disappointed at the lack of reliable tests for the early detection of recurrence, even though there are no data to suggest that detection of asymptomatic recurrences a few weeks or months earlier is of any benefit. It seems reasonable that identifying resistance to a new therapy and progression of disease at the earliest moment would avoid needless toxic effects of therapies doomed to fail and would permit earlier initiation of other potential therapies. Finally, the means of estimating overall prognosis for patients with metastatic breast cancer are few. These include tumor markers (e.g., expression of the estrogen receptor), performance measures, and crude measures of the extent of disease or the involvement of particularly ominous sites such as the brain and leptomeninges.

Sadly, patients with symptomatic, clinically detectable metastatic breast cancer are rarely cured. Clinicians consider stopping one treatment and changing to an alternative regimen for one of two reasons: unacceptable toxicity or progressive disease indicative of treatment resistance. The former is determined by history taking, and the latter is assessed by serial clinical evaluation of symptoms and estimates of tumor burden by means of radiologic imaging and blood measurements. Unfortunately, clinical evaluation is not very accurate in determining the response to treatment or the progression of disease, and serial radiographic imaging is expensive, time-consuming, inconvenient, and often inconclusive and may not be informative for many months after treatment initiation. Standard serologic tests, such as liver-function tests, are notoriously inaccurate. Circulating soluble-tumor-associated protein biomarkers, such as carcinoembryonic antigen and MUC1 (measured by the cancer antigen [CA] 15-3 and CA 27.29 assays), have reasonable sensitivity, but changes in levels don’t always reflect tumor response or progression and can be misleading. Recently, assays of circulating tumor cells have been shown to be prognostic before initiation of a new regimen; more important, failure to clear or reduce the number of circulating tumor cells suggests a poor response and the likelihood of rapid progression.

Thus, the development of new technologies, such as those now described in the Journal by Dawson et al., is of particular interest. The authors used two new methods to measure circulating DNA that could be directly linked to the primary tumor of the patient through specific mutations and structural variations found in the primary tumor but not in constitutive DNA. The most positive and encouraging result of this study was the demonstration that when mutations could be detected in the primary tumor and subsequently in the plasma, the variation in the number of copies of circulating tumor DNA was reasonably correlated with responses to treatment. In addition, there was a significant relationship between the number of copies in blood and the ultimate prognosis of the patient.

However, there are a number of caveats. Mutations or structural variants that could be tracked were found in only about 60% of patients. All patients with breast cancer have mutations in their tumor DNA, but without very intensive sequencing strategies, a specific probe or probes for each patient may remain elusive or very costly. This is in contrast to other cancers, in which either very common translocations or point mu-
tations might permit more successful application of this strategy. In fact, although Dawson et al. found that mutations in PIK3CA and TP53 are reasonably common in breast cancer (an analysis of tumor tissue revealed that 25 of the 52 patients carried a mutation in one of these genes), there is no single locus that is commonly mutated. Therefore, very substantial sequencing will be required for probe design; a standard “panel” is unlikely to work for all patients. Many tumors will require some form of sequencing. To wit, Dawson et al. observed that, on whole-genome sequence analysis, eight of nine patients carried structural variants other than PIK3CA and TP53, a finding that allowed the researchers to assay circulating tumor DNA in five additional patients (three had concomitant mutation of PIK3CA or TP53).

The number of patients with an objective response of circulating tumor DNA to treatment was limited, so the laudable effort to compare the usefulness of circulating tumor DNA with more standard measures such as circulating tumor cells and measures of CA 15-3 was more encouraging than definitive. And of course, many patients have readily measurable lesions that are effectively and cheaply assessed by means of physical examination or imaging. In an era of financial stressors on clinical care, the cost-effectiveness of such new methods will require rigorous study.

Despite these concerns, there is remarkable potential for this approach. Complete pathological remissions in patients treated with neoadjuvant therapies are not only reliably predictive of better outcomes but also were recently proposed by the Food and Drug Administration as a valid surrogate for drug approval. Nonetheless, some patients in whom a complete pathological remission is achieved eventually have a relapse, whereas others in whom such a remission is not achieved never have a recurrence. Perhaps assays of circulating tumor DNA, which has an impressive dynamic range, could more reliably predict patients who might not need further therapy or identify those with localized breast cancer who would be adequately treated by lumpectomy alone. The apparent high sensitivity of the assay suggests that it might be used to screen for recurrences in asymptomatic patients with previously diagnosed early-stage disease — although this potential use has not been proven to improve patient outcomes. Finally, identification of new mutations in circulating tumor DNA over time might inform the clinician about tumor evolution and provide evidence to support new treatment targets not identifiable in the primary tumor.

In summary, the new study provides proof of the concept that circulating tumor DNA represents a sensitive biomarker of tumor burden. Demonstration that the method can be used to take better care of patients with metastatic breast or other cancers in a cost-effective manner awaits further studies, which are clearly warranted.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

From the Leonard M. Miller School of Medicine, University of Miami, Miami (M.L.), and the Breast Center at Baylor College of Medicine, Houston (C.K.O.)

This article was published on March 13, 2013, at NEJM.org.


DOI: 10.1056/NEJMMe1301249

Copyright © 2013 Massachusetts Medical Society.