Predicting survival in advanced breast cancer has a long and problematic history. Both physicians and patients care about survival prediction, although for somewhat different reasons. The patient’s interest springs from the most human of motives: how long have I got? Will I see my child graduate from school? Will I live to see the birth of my grandchild? Physicians naturally wish to provide patients guidance on these matters, and in addition, find prognostic information useful in determining appropriate therapeutic options.

Unfortunately, physicians have never been very good at predicting survival. Breast cancer is a disease with sometimes astonishing heterogeneity with regard both to natural history and therapeutic response. Indeed, therapeutic response and natural history entwine to a confusing degree. In addition, the rapidly evolving therapeutic landscape can render older prognostic categorization irrelevant; compare the fate of the HER2-positive patient a decade ago versus today.

This issue’s article by Budd and colleagues (1) represents an attempt to solve the prognostication problem through the application of a novel technology. It is one of several recent articles from the same group of investigators examining the role of circulating tumor cells (CTC) in patients with advanced disease (2, 3). To summarize this work, the presence of high CTC counts (≥5 per 7.5 mL of whole blood) is associated with shorter progression-free and overall survival in the metastatic setting, and their continued presence following the initiation of a new therapy similarly predicts impaired therapeutic response and overall survival.

The current article extends the prior work by comparing CTC measurement with standard radiographic measures of disease progression as prognostic indicators. The population of patients studied was receiving either front-line or second-line therapy for metastatic disease, all with measurable disease. It is a representative population with regard to estrogen receptor and HER2 status, but unrepresentative in having few patients with bone-only metastatic disease (a function of the requirement for radiographically measurable disease).

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In this study, both CTC and radiographic measurements provided independent prognostic information. CTC measurements obtained 4 weeks after the initiation of therapy clearly provided independent prognostic information useful in determining appropriate therapeutic options. The study raises questions as well as answering them, some of which are discussed below.

What do CTC measurements really measure? At its simplest level, the assay used in this study measures circulating cells that express epithelial cell adhesion molecule (EpCAM). In primary and metastatic breast cancers, EpCAM is expressed at levels that are 100- to 1,000-fold greater than in benign epithelial cells, and is implicated in tumor invasion and migration (4). EpCAM has been suggested as a potential therapeutic target for patients with advanced malignancies, with clinical trials of anti-EpCAM antibodies having been done in breast cancer (5).

With regard to CTC measurements, however, a deeper level question should be asked: what does it mean to have circulating EpCAM-positive cells? There are two possible answers to this question. CTC measurements could reflect the volume of metastatic disease in the patient with breast cancer, or they could reflect tumor biology (a summation of factors such as aggressiveness, drug resistance, and mutation).

In this and previous studies, tumor load, as measured radiographically, did not correlate with CTC measurements, with the caveat that radiographic measurements are not a perfect surrogate for tumor volume (nor even particularly reproducible). In contrast, this and other studies suggest that the presence of EpCAM-positive CTCs denotes the presence of aggressive pathobiology.

What are the benefits and disadvantages of CTC measurement? The benefits of CTC measurements, as used in this review, are straightforward. The technique employed was highly reproducible and standardized across multiple sites. Indeed, the reproducibility of CTC measurement in the Budd study, as opposed to that of standard radiographic techniques (even in the hands of expert radiologists), is striking. Assay reproducibility has been the downfall of many a prognostic factor, and the care given to this issue is to be congratulated. The disadvantages of the technique represent the opposite side of the coin: reproducibility is dependent on the use of proprietary technology, and the use of this technique does not replace (at least at present) standard radiographic examination. Routine use of this approach would therefore increase the cost of patient evaluation.

Does finding out bad news earlier really help? The old Baconian dictum that “knowledge is power” appeals to many clinicians and patients. Early discovery of tumor progression might allow earlier therapeutic intervention with follow-on therapy, leading to improved patient outcome. Although an appealing concept, there is no current data supporting this approach. The use of (admittedly crude) radiographic and serologic measures of metastatic disease in the postadjuvant setting failed to improve overall survival when compared with minimalists follow-up in two large randomized trials (6, 7). Similarly, cancers that progress early on front-line chemotherapy frequently have multidrug-resistant phenotypes and lower.
response rates to second-line chemotherapy compared with cancers undergoing initial disease response. Therefore, we lack any compelling data to suggest that measurement of CTCs will improve outcome. What we are left with is the possibility that finding failure at an early point in time will decrease the toxicity and eliminate the expense of ineffective agents.

What is the future of CTC measures? I have argued above that finding bad news earlier does not make the news less bad. Useful early intervention depends on the existence of effective agents specific to the patient’s cancer. CTC measures that would allow therapeutic individualization represent at least a partial approach to this problem. An initial example of this approach is provided by the analysis of CTC HER2 expression, in which recent work has suggested the conversion from HER2 negativity in the primary tumor to HER2 positivity in circulating cancer cells (8, 9). It is unknown whether this conversion can be turned to clinical advantage. Similarly, a test that would predict benefit to a specific chemotherapeutic agent (e.g., “agent A is failing the patient; use agent B” or “eliminate agent A from combination A + B; it adds nothing”) would offer enormous cost savings and prevent significant unwanted toxicity. The increasing ability of modern molecular biology techniques to pull more and more data out of smaller and smaller numbers of cancer cells bodes well for progress in this area.

The Breast Cancer Intergroup of North America currently plans to study the role of CTCs in a prospective randomized trial (S0500). This trial will test the strategy of changing or maintaining therapy for patients with metastatic breast cancer based on elevated CTC measurements after the first cycle of chemotherapy. S0500 will evaluate overall survival as its primary end point, and as such, will measure the most clinically important patient benefit of therapy. If successful, it may show us whether the “blood will tell” an important predictive truth.

References
Circulating Tumor Cells in Breast Cancer: Blood Will Tell

George W. Sledge, Jr.


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