Anthracycline War: No Victor Yet

By Patrick Young

Thirty years ago, the introduction of anthracyclines, such as doxorubicin and epirubicin, gave oncologists a more effective cytotoxic agent and commenced the drugs’ long reign as the foundation of early breast cancer therapy. But some experts now argue that with the advent of newer drugs—trastuzumab (Herceptin) and the taxanes, such as paclitaxel (Taxol) and docetaxel (Taxotere)—there is little use for anthracyclines in early disease. Others strongly disagree.

At the heart of the controversy is recent evidence suggesting that anthracyclines may work only in women who have extra copies of the HER2 protein or overexpression of the gene. The strength of this evidence is disputed, but if its proponents turn out to be right, it could mean that anthracyclines might not be needed in any form of early breast cancer: If the drugs work only in HER2-positive patients, then it would add no benefit for women with normal levels of HER2 (often referred to as HER2 negative), who are treated with taxanes. And HER2-positive patients wouldn’t need anthracyclines, the argument goes, because it adds no benefit to trastuzumab, which targets HER2, and taxanes.
“I have little doubt that in 5 years relatively few women with early breast cancer will be treated with anthracyclines,” said Stephen Jones, M.D., of Texas Oncology in Dallas. Jones led U.S. Oncology Research Trial 9735, a key study suggesting that anthracyclines added no benefit to taxane-based regimens in early breast cancer. He serves as an adviser to Sanofi Aventis, maker of docetaxel.

This argument has received a good amount of publicity, and anecdotal evidence suggests that anthracycline use is declining. The Jonsson Cancer Center at the University of California, Los Angeles, for instance, stopped using anthracyclines for first-line breast cancer treatment in 2007. That same year, the National Breast Cancer Coalition took the position that “for the vast majority of women with breast cancer, anthracycline-based chemotherapy is no more effective and has the potential for more serious toxicities than other known regimens.” Oncologists report that colleagues are decreasing their use of the drugs, and some estimates suggest an approximately 50% decline in purchases by community oncologists.

But other experts urge caution. “The problem is,” said Clifford A. Hudis, M.D., of Memorial Sloan–Kettering Cancer Center in New York, “that all the work so far on anthracyclines versus nonanthracyclines has been done either in unselected [patients for HER2 status in] prospective trials or retrospectively.” In an educational session at this year’s annual meeting of the American Society of Clinical Oncology (ASCO), Hudis argued that the evidence from both kinds of studies is limited. He concluded that, for now, anthracyclines remain the backbone of chemotherapy for early breast cancer, whether it is HER2 positive or HER2 normal.

**HER2-Normal Patients**

Interest in dropping anthracyclines from chemotherapy regimens stems from concerns about the drugs’ adverse effects, including congestive heart disease and, in the long term, myelodysplastic syndrome and leukemia. One of the most recent trials to test anthracyclines versus no anthracyclines was U.S. Oncology’s 9735 trial, which randomized 1,016 women to four cycles of docetaxel–cyclophosphamide or doxorubicin–cyclophosphamide. At 7 years’ median follow-up, there was a statistically significant improvement in disease-free and overall survival in the taxane (docetaxel) arm compared with the anthracycline (doxorubicin) arm.

Skeptics argue that the number of patients in the trial was too small to support a major revision in first-line anthracycline use. They also question whether the four cycles of chemotherapy was optimal, considering that 52% of the patients had node-positive disease. The standard of care for high-risk, node-positive patients is now six to eight cycles of chemotherapy with both anthracyclines and taxanes.

Other trials are now looking at the anthracycline-versus-taxane question with different regimens.

A report 3 years ago in the *New England Journal of Medicine* by Kathleen Pritchard, M.D., of the Sunnybrook Odette Cancer Centre in Toronto, and colleagues, supported the argument that anthracyclines are not necessary, at least in HER2-normal patients. This retrospective analysis of tumor tissues from patients enrolled in early breast cancer trials found that the benefits of anthracyclines were limited to HER2-positive patients; the HER2-normal patients did not benefit. More recently, a meta-analysis of 5,354 early breast cancer patients with known HER2 status, led by Alessandra Gennari, M.D., Ph.D., of Italy’s National Cancer Research Institute in Genoa, came to a similar conclusion (J. Natl. Cancer Inst. 2008;100:14–20).

But there are conflicting data. A recent retrospective analysis of a Scottish trial, BR9601, showed that adding an anthracycline to conventional chemotherapy benefited only the HER2-normal women. John Bartlett, Ph.D., and colleagues at the Edinburgh Cancer Research Centre found that HER2-normal women who received an anthracycline in addition to the conventional CMF (cyclophosphamide, methotrexate, and fluorouracil) chemotherapy had improved overall survival compared with those who received CMF alone.

In hopes of finally resolving these issues, the National Surgical Adjuvant Breast and Bowel Project and U.S. Oncology Research have just opened a prospective, randomized, controlled trial (NSABP B-46/USOR 7132) with three arms: Docetaxel–cyclophosphamide plus bevacizumab will be compared to docetaxel–cyclophosphamide alone and to docetaxel, doxorubicin, and cyclophosphamide. The researchers expect to accrue 3,900 HER2-normal patients with resected node-positive or high-risk node-negative breast cancer over 32 months and will monitor them for 10 years. Their primary objective is to determine whether the addition of bevacizumab improves invasive-disease–free survival. But a secondary objective is to determine the difference in survival between the anthracycline-based and taxane-based regimens.

**In HER2-Positive Patients**

Meanwhile, controversy also continues over use of anthracyclines in HER2-positive breast cancers. One of the primary triggers of this debate was a Breast Cancer International Research Group trial, known as BCIRG 006, headed by UCLA’s Dennis Slamon, M.D., Ph.D., who developed trastuzumab and holds related patents. The results showed that adjuvant trastuzumab plus docetaxel in HER2-positive early breast cancer reduced the risk of recurrence by one-third and increased overall survival by 34%. Women in the trial who received an anthracycline in addition to trastuzumab and the taxane had outcomes no different from those who
received trastuzumab and taxane with a platinum drug. On the basis of these results, the U.S. Food and Drug Administration approved trastuzumab for adjuvant treatment of early breast cancer, in combination with other drugs, with or without an anthracycline.

Given the toxicity of anthracyclines and the availability of trastuzumab, Slamon and others argue that treatment regimens should not include anthracyclines. “If you get the equivalent benefit [with trastuzumab] but not the toxicity,” said Slamon, “there is no reason to use the anthracyclines unless a woman is somewhere in the world where she can’t get one of the targeted therapies.”

But others argue that the preponderance of the evidence still favors using anthracyclines, along with trastuzumab and taxanes, in HER2-positive patients. Hudis pointed out that although five major randomized, controlled trials, including BCIRG 006, have demonstrated the benefits of trastuzumab in HER2-positive patients, almost all patients in those trials also received an anthracycline.

The data suggesting that anthracyclines offer no additional benefit to trastuzumab are limited and contradictory, he said. “They simply don’t all come to the same conclusion.”

**Topoisomerase II Alpha**

The trastuzumab-versus-anthracycline debate has grown more complicated with evidence that another gene, a neighbor of HER2, actually accounts for the benefits of anthracyclines in HER2-positive patients. In one of the most recent studies, Pritchard and colleagues reported that women with topoisomerase II alpha (TOP2A) gene alterations showed an increased responsivity to anthracycline-based regimens compared with nonanthracycline treatments. The benefit was similar to that observed in HER2-positive patients. (J. Natl. Cancer Inst. 2009;101:644–650).

In an accompanying editorial, Slamon and Michael F. Press, M.D., Ph.D., at the University of Southern California, concluded that the Pritchard analysis adds to the evidence demonstrated that anthracyclines benefit only HER2-positive breast cancer patients (who don’t need them because they’ve got trastuzumab).

“One of the things coming out of this paper is that you don’t get TOP2A alterations without HER2,” Slamon said. “This paper is the latest to drive a nail in the coffin of people who want to push these anthracycline-based therapies.”

But Pritchard questions whether HER2 and/or TOP2A provide a treatment marker as reliable as commonly assumed. “In my opinion, we don’t know if we can select patients for anthracyclines or not based on HER2 or TOP2A,” she said. “Our idea has been that HER2 was just a neighbor and TOP2A was the explanation. That made scientific sense because anthracyclines are known to attack topoisomerase, but it may be something else.”

Adding to the uncertainty are issues surrounding the assays used to detect TOP2A amplification. Heather L. McArthur, M.D., Hudis, and colleagues presented evidence at last year’s San Antonio Breast Cancer Symposium that commercially available FISH (fluorescence in situ hybridization) probes may overestimate the frequency of TOP2A amplification in tumors with amplified HER2. Using a different assay, called ROMA (high-resolution representation oligonucleotide microarray analysis), they found that coamplification of HER2 and TOP2A to similar degrees was uncommon.

“We think this discrepancy may relate to the accuracy of FISH probes and the extent of coamplification,” Hudis said. “The probes can be wider than the gene of interest. This doesn’t mean there isn’t something else important in the region that is being picked up that is critical.” In fact, another study presented at ASCO by Christine Desmedt, Ph.D., of the Jules Bordet Institute in Brussels, found that variation, not only in TOP2A but also in a group of nearby genes, predicted response to anthracyclines.

“Complicated? Yes!” said Hudis in his ASCO presentation. “The point that I’d like to make is that one should shy away from too much dogma in this arena.”