In this issue of the Journal, Gennari et al. (1) report results of a meta-analysis of eight published studies that tested the worth of HER2 as a predictive marker of benefit from anthracycline regimens over nonanthracycline regimens. The test for treatment by HER2 status interaction yielded statistically significant results. The authors propose that it is time to stop the use of cardiotoxic anthracycline regimens for the treatment of HER2-negative breast cancer.

Most investigations of predictive markers in the adjuvant setting have suffered from a lack of statistical power because the original trials were sized to test the efficacy of the treatment on the whole cohort rather than on the subsets defined by the markers (2). Likewise, the individual studies included in the meta-analysis lacked sufficient statistical power to convincingly demonstrate an interaction between HER2 and anthracyclines. Meta-analyses of marker studies such as the one conducted by Gennari et al. (1) are a welcome addition to the literature.

The initial study that fueled interest in this question, which was conducted by Gusterson et al. (3), suggested that patients with HER2-positive tumors derive less benefit from perioperative treatment with a cyclophosphamide, methotrexate, and 5-fluorouracil regimen than those with HER2-negative tumors. The hypothesis that HER2-positive tumors were resistant to chemotherapy supported the concept that targeted therapies would need to be developed to address this problem. Preclinical studies showing that overexpression of HER2 induced resistance to cisplatin (4) as well as demonstrating the synergistic effects of an anti-HER2 antibody and cisplatin provided further support for this hypothesis (5). However, results from Cancer and Leukemia Group B (CALGB) trial 8869 showing that the selective benefit from standard-dose cyclophosphamide, doxorubicin, and 5-fluorouracil (CAF) over lower dose CAF appeared to be limited to patients with HER2-positive tumors led to an alternative hypothesis, that HER2-positive tumors derive selective benefit from anthracyclines or have an increased response to higher potency chemotherapy in general due to their higher proliferation rate (6).

As described by Gennari et al. (1), many groups subsequently attempted to evaluate the selective benefit of anthracycline-containing regimens for HER2-positive tumors. When trials to test the worth of adding trastuzumab to chemotherapy were being designed, inclusion of anthracyclines in the chemotherapy regimen was an important issue because of potential cardiotoxicity from the anthracycline-trastuzumab combination. Due to the available evidence suggesting that HER2-positive tumors were sensitive to anthracyclines, doxorubicin and cyclophosphamide (AC) followed by paclitaxel was chosen as the chemotherapy regimen for the trastuzumab trials conducted by the National Surgical Adjuvant Breast and Bowel Project and the US Intergroup (7). However, in the Breast Cancer International Research Group 006 trial, investigators decided to include a nonanthracycline investigational arm based on preclinical observations of synergy between platinum-based chemotherapy and trastuzumab (8) and decided to compare docetaxel, carboplatin, and trastuzumab (TCH) with AC followed by docetaxel (ACT) without or with trastuzumab (ACTH). Results of the second interim analysis, which were reported at the 2006 San Antonio Breast Cancer Symposium, suggest that clinical outcome of patients treated with TCH was similar to that of patients treated with ACTH (9). Furthermore, a US Oncology trial demonstrated the superiority of docetaxel plus cyclophosphamide (TC) over AC in patients who were not selected by HER2 status (10). These data suggest the possibility that anthracyclines are no longer necessary in the adjuvant treatment of breast cancer. A recent report of long-term cardiotoxic effects associated with the use of anthracyclines in the adjuvant setting has further supported this belief (11).

However, before we abandon anthracyclines as a component of our adjuvant chemotherapy regimens, we need to critically review the available data in light of our current understanding of the molecular heterogeneity of breast cancer. For example, we now know that molecular heterogeneity exists within both HER2-positive and HER2-negative tumors, which is associated with differing sensitivity to chemotherapy. Although molecular heterogeneity can be defined in variety of ways, for the sake of this discussion we will use the terminology describing the so-called intrinsic subtypes of breast cancer as defined on the basis of gene expression by Perou et al. (12).

Both HER2 and basal-like subtypes of breast cancer are more sensitive to chemotherapy compared with the luminal subtypes (13,14). This difference may be due to the higher levels of proliferation and the lower estrogen receptor levels that are generally present in the former tumor subtypes (12). The HER2 subtype is characterized by HER2 gene amplification and subsequent coordinated overexpression of HER2 protein along with other genes in the long arm of chromosome 17 that coamplified with the...
HER2 gene. Because the size of the amplicon varies among tumors, some genes, such as the gene encoding topoisomerase II alpha (topo2) are not always coamplified and co-overexpressed with HER2 (15). Because HER2 itself was not associated with chemosensitivity in vitro (16,17), from a mechanistic viewpoint the dominant hypothesis is that topo2 is the actual target for anthracyclines and that HER2 amplification and/or overexpression is simply a surrogate for topo2 expression. However, the data from clinical trials linking topo2 gene amplification with selective benefit from anthracyclines remain weak because of small sample sizes (18,19). So the question of whether HER2-positive tumors are sensitive to anthracyclines because they express more topo2 or simply because they have a higher proliferation rate remains unanswered. It is intriguing that Muller et al. (20) could not demonstrate an association between amplification of the topo2 gene and the level of topo2 protein but instead found a strong association of topo2 protein level with proliferation markers and histologic grade. We have validated this finding in an unpublished study of 740 patients (S. Paik, MD, Y. Taniyama, MD, unpublished observations). These findings support the hypothesis that the increased sensitivity of HER2-positive breast cancers to anthracyclines is related to their higher proliferation rate. The recent CALGB study demonstrating that the benefit from administering paclitaxel following AC appeared to be restricted to the HER2-positive or estrogen receptor–negative cohorts further supports this hypothesis (21). In that regard, given the high proliferation rate associated with the basal-like subtype, it may be premature to abandon anthracyclines altogether. In support of this argument, Carey et al. (13) found a similarly higher sensitivity to neoadjuvant AC in the HER2 and basal-like subtypes compared with the luminal subtypes (pathologic complete responses rates = 36%, 27%, and 7%, respectively).

On the other hand, the adjuvant trial conducted by Jones et al. (10) demonstrated that substitution of docetaxel for doxorubicin improved the outcome of adjuvant therapy patients who were unselected by HER2 or hormone receptor status. These results do not address the question of whether the addition of doxorubicin to TC (TAC) will be superior to TC in patients diagnosed with HER2-negative cancers, especially the basal-like subtype of these cancers. This question needs to be addressed in a randomized clinical trial before we completely abandon the use of anthracyclines in the adjuvant setting. Fortunately, the US Oncology Research Group has initiated a trial that compares TC with TAC in women diagnosed with operable HER2-negative breast cancer to directly test this question and is actively pursuing collaboration with other investigators to insure the success of the study. Until results from the US Oncology trial become available, it may be reasonable to use TC as the baseline chemotherapy regimen for trials testing the worth of targeted therapies that may have potential cardiotoxic effects as suggested by the available data.

It is important to recognize, however, that a large subset of women with HER2-negative and estrogen receptor–positive tumors may not benefit from any chemotherapy (22). Therefore, optimization of adjuvant chemotherapy for patients diagnosed with breast cancer will depend on defining the baseline prognosis and chemosensitivity of each subclass of breast cancer beyond those crudely defined by HER2 status alone (13,14,22). In some sense, the meta-analysis by Gennari et al. (1) may already have only historical importance in this rapidly evolving field. For patients, however, that is great news.

References

