

## EDITORIALS



## Adjuvant Chemotherapy for Breast Cancer — 30 Years Later

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In 1976, Bonadonna and his colleagues published the results of their landmark trial of adjuvant chemotherapy for breast cancer.<sup>1</sup> They showed that 12 months of postoperative chemotherapy consisting of cyclophosphamide, methotrexate, and fluorouracil (CMF) decreased the risk of recurrence of breast cancer in women with positive axillary lymph nodes. Since then, many trials have been undertaken to answer important questions about adjuvant chemotherapy: What is the optimal number of drugs? What are the most advantageous doses of the agents used for adjuvant chemotherapy? How long should they be administered? Does the inclusion of an anthracycline improve the outcome? In many of these trials, CMF was the standard therapy.

The meta-analysis reported by the Early Breast Cancer Trialists' Collaborative Group in 1998 showed that, as compared with CMF, anthracycline-containing chemotherapy was associated with significant reductions in the rates of recurrence and death. In individual trials, CMF and doxorubicin plus cyclophosphamide were equivalent in terms of relapse-free and overall survival,<sup>2</sup> whereas cyclophosphamide, epirubicin, and fluorouracil-containing regimens were superior to CMF.<sup>3</sup> Perhaps the failure to detect an advantage of doxorubicin plus cyclophosphamide over CMF was due to the short duration of treatment with doxorubicin plus cyclophosphamide. In any case, the 2000 National Institutes of Health Consensus Development Conference on Adjuvant Therapy for Breast Cancer recommended anthracycline-containing regimens for the adjuvant treatment of breast cancer.

In general, an anthracycline — whether doxorubicin or epirubicin — is incorporated into a CMF regimen by administering it instead of

methotrexate in CMF or by adding it either before or after the administration of CMF. In this issue of the *Journal*, Poole et al. report on a trial of adjuvant chemotherapy for early breast cancer in which four cycles of epirubicin given every 3 weeks, followed by four cycles of CMF, were compared with eight cycles of CMF alone.<sup>4</sup> This experimental regimen was based on a trial in Milan that compared four cycles of doxorubicin followed by eight cycles of CMF with a 2:1 alternating regimen of the same drugs.<sup>5</sup> The control group in the Italian trial did not receive CMF; thus, the trial by Poole and his colleagues better reflects the advantage (or disadvantage) of adding an anthracycline to CMF. The results of the trial reported by Poole et al., at a median follow-up of 48 months, showed that the administration of epirubicin followed by CMF improves relapse-free and overall survival as compared with the administration of CMF alone.

The trial reported by Poole and colleagues combined the results of two independent trials, the National Epirubicin Adjuvant Trial (NEAT) and the BR9601 trial. This combination of data sets is somewhat unusual, but it was specified a priori, and the clinical characteristics of the participants in the two trials were very similar. In both trials, four cycles of epirubicin were given before the administration of four cycles of CMF. The schedule and duration of chemotherapy regimens within each trial were similar. Although the CMF regimens differed in the two trials (as explained in the article, classic CMF was used in NEAT, whereas a modified CMF regimen was used in the BR9601 trial), whether any differences between NEAT and the BR9601 trial influenced the combined results reported by Poole et al. is difficult to determine. It is reassuring, however, that

85% of the patients were enrolled in the NEAT trial, which used classic CMF, and the benefit of the sequential regimen was seen in both trials. The report by Poole and colleagues does not include the number of patients in each group who received adjuvant radiation therapy or tamoxifen during follow-up. Both of these therapies can reduce the risk of recurrence and death from breast cancer. A subgroup analysis showed that there was no significant difference in outcomes for women with estrogen-receptor-positive tumors. Longer follow-up will show whether a difference in this subgroup emerges.<sup>6</sup> Although alopecia, nausea, and vomiting were more frequent with epirubicin followed by CMF than with CMF alone, these adverse effects were tolerable.

The structural differences between epirubicin and doxorubicin may account for the different safety profiles of the two agents; at the same dose, epirubicin has a lower degree of toxicity than doxorubicin.<sup>3</sup> This therapeutic advantage allows for an escalation of the dose of epirubicin. Regimens that have shown a clear benefit over CMF have contained epirubicin<sup>3,4</sup> rather than doxorubicin.<sup>2,7</sup>

Recent trials of adjuvant chemotherapy have examined how best to incorporate taxanes (paclitaxel and docetaxel) into anthracycline-containing regimens. The addition of four cycles of paclitaxel after the administration of doxorubicin plus cyclophosphamide was associated with a better outcome than doxorubicin plus cyclophosphamide alone,<sup>8</sup> and a dose-dense regimen consisting of four cycles of paclitaxel after doxorubicin plus cyclophosphamide (administered every 2 weeks) was better than the standard schedule of doxorubicin plus cyclophosphamide followed by paclitaxel.<sup>9</sup> In another trial, the substitution of docetaxel for fluorouracil in a regimen that included doxorubicin and cyclophosphamide improved the outcome.<sup>10</sup> Two recent trials showed an improved outcome of sequential therapy with an anthracycline and a taxane as compared with an anthracycline alone.<sup>11,12</sup>

Where are we in 2006 with respect to adjuvant chemotherapy for breast cancer? We know that adjuvant chemotherapy reduces the risk of recurrence and increases the rate of survival among women with early breast cancer, but the magnitude of the benefit is modest, and many patients have to be treated to benefit a few. Adjuvant chemotherapy is associated with considerable toxic

effects and costs to the health care system. When caring for a woman with early breast cancer, the physician needs to consider the risk of recurrence on the basis of the presence or absence of tumor in the axillary nodes as well as the size and grade of the tumor and *HER2* (human epidermal growth factor receptor type 2) status. The physician also must consider the endocrine responsiveness of the tumor. Effective communication between the patient and the physician is essential, and the patient should be encouraged to participate in the decision-making process. The benefits and risks of treatment must be explained.

The usual approach is to tailor the aggressiveness of the chemotherapy to the risk of recurrence. As compared with standard chemotherapy, aggressive chemotherapy is associated with a greater benefit, but also with more acute and long-term toxic effects such as leukemia and heart failure. Hence, patients at high risk for recurrence might be offered a regimen that includes an anthracycline and a taxane<sup>8-10</sup> or an intensive anthracycline regimen.<sup>3,4</sup> Patients at lower risk for recurrence might be offered a less aggressive regimen with fewer side effects (such as CMF or doxorubicin plus cyclophosphamide) or perhaps just endocrine therapy alone. CMF alone is an option for women who cannot receive an anthracycline.

Considerable progress has been made in the fight against breast cancer, but there is still much to be done. The addition of trastuzumab after chemotherapy is a recent exciting development.<sup>13</sup> Promising new agents such as bevacizumab and lapatinib need to be tested, and additional agents developed. Important advances are also being made in the use of genetic analyses to determine the risk of recurrence and to predict a tumor's responsiveness to chemotherapy.<sup>14,15</sup> Thus, adjuvant therapy that is tailored for the patient who is most likely to benefit on the basis of amplification of a particular gene or gene profile may be just around the corner.

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## When the Failing, End-Stage Heart Is Not End-Stage

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Heart failure is increasing in incidence and prevalence, is expensive to treat, and is associated with substantial morbidity and mortality.<sup>1</sup> In the nomenclature of the guidelines of the American Heart Association and the American College of Cardiology, the majority of patients with heart failure are classified as having stage C heart failure, characterized by structural heart disease that is or has been symptomatic.<sup>2</sup> Numerous drugs (e.g., angiotensin converting-enzyme [ACE] inhibitors or angiotensin-receptor blockers, beta-blockers, and aldosterone blockers) and electrophysiological devices may temporarily halt, slow, or even reverse the pathophysiological processes in patients with stage C heart failure. Reversion of the heart toward more normal shape and function is called reverse remodeling.

Yet the course of heart failure in many patients is generally an inexorable downward spiral (Fig. 1). The repetitive and iterative physiological derangements eventually result in refractory, end-stage disease (stage D heart failure). Life expect-

tancy for patients with stage D heart failure is short, with a 1-to-2-year survival rate of less than 50 percent. Medications that previously were beneficial are no longer so well tolerated. Cardiac-resynchronization therapy in this setting is rarely, if ever, even palliative. End-of-life strategies, transplantation, or support with a left ventricular assist device — intended as permanent or “destination” therapy — is required.<sup>3</sup> Spontaneous reversal of stage D heart failure is unusual.

Nevertheless, some reports indicate that intervention can modify progression, suggesting that stage D heart failure does not always represent a point of no return. For instance, in one study of patients with severe heart failure in whom beta-blockers had adverse hemodynamic effects, the administration of a phosphodiesterase inhibitor (a positive inotropic agent) made possible the administration of appropriate doses of beta-blockers, with their known long-term myocardial and survival benefits.<sup>4</sup> Half the patients had improvement of a sufficient magnitude that the phospho-