Integration of Docetaxel Into Adjuvant Breast Cancer Treatment Regimens

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Adjuvant chemotherapy is an integral component of the multidisciplinary curative treatment of primary breast cancers. The experience of the last 3 decades indicates that anthracycline-containing regimens provide the most effective cytotoxic treatment for this purpose.

The introduction of adjuvant chemotherapy into treatment was based on improved understanding of the natural history and clinical course of breast cancer managed surgically during the first half of the 20th century.[1] This experience led to the increased realization that micrometastases were in existence in most patients at the time of initial diagnosis.[1,2] The initial reports were based on single-agent alkylating therapy,[2,3] followed shortly by clinical trials that used the CMF combination regimen of cyclophosphamide, methotrexate, and fluorouracil (5-FU) as an adjuvant therapy to surgical resection.[4] By 1980, most North American oncologists accepted adjuvant chemotherapy as a clinically beneficial intervention for premenopausal patients with axillary lymph node-positive breast cancer.

The Early Breast Cancer Trialists’ Collaborative Group established a database of all randomized clinical trials (whether published or not) of primary breast cancer. Meta-analyses of all available data explored the effect of systemic and locoregional therapies on odds of recurrence and mortality.[5-10] These meta-analyses, conducted at 5-year intervals starting in 1985, contributed substantially to the general acceptance of adjuvant systemic therapy as standard treatment.[7-9,11-12] By 1985, the clinical value of adjuvant tamoxifen was demonstrated, and by 1990, there was evidence that extended the indications of adjuvant chemotherapy and hormonal therapy to lymph node-negative breast cancer. A recent National Institutes of Health (NIH)-organized Consensus Development Conference on Adjuvant Therapy of Breast Cancer issued a comprehensive, evidence-based report on the status of adjuvant chemotherapy (available at http://odp.od.nih.gov/consensus/cons/114/114_intro.htm).

Individual studies, and especially the overview of randomized trials, demonstrated the value of ovarian ablation (whether surgical, chemical, or radiation-induced) in reducing risk of recurrence or death for premenopausal patients.[5,11] The benefits from ovarian ablation appear similar to those of adjuvant chemotherapy and persist for at least 15 years after diagnosis. As is the case for all hormonal therapy, the benefits of ovarian ablation are limited to women with estrogen receptor-positive breast cancer. Mature evidence from individual trials and the overview not only confirmed the value of tamoxifen in reducing risk of recurrence and death, but also demonstrated that the effects of this intervention persist 10, and probably 15, years beyond diagnosis.[5,12] The optimal duration of tamoxifen therapy appears to be 5 years.[13-15] For patients of any age with estrogen receptor-positive breast cancer, the combination of tamoxifen and chemotherapy provides greater benefits than either treatment alone.[5,12]

Review of randomized clinical trials of cytotoxic therapy prompts several conclusions. First, combination chemotherapy is clearly more effective than single-agent treatment.[5,7-9,16-19] The question of whether the most effective drugs should be combined simultaneously, or in sequence, is currently under evaluation.[20] Second, chemotherapy appears more effective for women under the age of 50 years than for those older than age 50.[7,9] Chemotherapy has both a cytotoxic and an endocrine effect in premenopausal patients, whereas the endocrine effect would be absent in postmenopausal women.[21-24] Lower than standard doses have been associated with inferior results.[25-27] The effect of adjuvant chemotherapy in women older than age 70 years has not been adequately tested.

The estrogen receptor status of the tumor is another factor that modifies the effect of adjuvant chemotherapy. There is a trend towards greater reductions in odds of recurrence and death for estrogen receptor-poor primary tumors than for estrogen receptor-rich tumors.[7-9] These
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While several drugs and drug combinations have been used for adjuvant chemotherapy, most first-generation clinical trials utilized a combination of cyclophosphamide, methotrexate, and 5-FU (CMF). Evidence from second-generation trials supported the use of anthracycline-based therapy as the treatment of choice for most patients.\[9\] The use of doxorubicin (Adriamycin) or epirubicin (Ellence) in combination with other agents provided greater benefit than combinations without anthracyclines.\[28\]

The AC regimen (doxorubicin [Adriamycin]/cyclophosphamide [Cytoxan, Neosar]) has been readily adopted in North America because of its ease of administration. There is no evidence, however, that this regimen is any better than CMF or that it is equivalent to more widely tested combinations, such as FAC (fluorouracil [5-FU]/doxorubicin [Adriamycin]/cyclophosphamide [Cytoxan]) or FEC (5-FU/epirubicin/cyclophosphamide), each of which has been shown to be superior to the classic CMF regimen (http://odp.od.nih.gov/consensus/cons/114/114_intro.htm).

Regardless of the regimen used, four to six cycles of therapy provide optimal results when using one, nonsequential combination; shorter treatment durations might be less effective.\[29,30\] Fixed crossover regimens, using two different combinations, are under evaluation today and require longer durations of treatment.\[31-33\]

The Role of Taxanes in Adjuvant Therapy

The role of taxanes in the adjuvant therapy of breast cancer is under intense investigation. Two consecutive analyses of a large randomized Cancer and Leukemia Group B trial (CALGB 9344) in node-positive patients designed to test whether four cycles of paclitaxel following four cycles of AC improved the results of four cycles of AC demonstrated a small but significant reduction in odds of recurrence and death for the paclitaxel-containing arm. The results of the third analysis of this trial, presented at the recent Consensus Development Conference, showed a quantitative reduction in this benefit, while the qualitative advantage persisted for the paclitaxel-treated group. Results demonstrate that the absolute differences in recurrence rates and survival rates were maintained, but relative improvement in survival end points are becoming less significant. Two other randomized trials (National Surgical Adjuvant Breast and Bowel Project [NSABP] and The University of Texas M. D. Anderson Cancer Center) also designed to test the role of taxanes in the adjuvant chemotherapy of breast cancer, failed to show, as yet, a significant advantage for the paclitaxel group.

A policy of optimal locoregional therapy combined with an anthracycline-containing chemotherapy regimen and hormone therapy targeted to patients with hormone receptor-positive tumors should result in a 40% to 60% relative reduction in risk of recurrence and a 40% to 50% relative reduction in mortality when compared with surgical therapy alone. While this represents substantial progress, there is still much room for improvement. Therefore, incorporation of new and effective antitumor agents into the curative regimens used for adjuvant systemic therapy is a very high priority.

Docetaxel in Adjuvant Chemotherapy of Breast Cancer

Docetaxel (Taxotere) is a tubulin-active antitumor agent with substantial activity against breast cancer.\[34-36\] When used as a single agent, docetaxel produces overall response rates ranging from 50% to 70% in groups of patients previously unexposed to chemotherapy; in anthracycline-resistant patients, docetaxel retains a high level of activity, with response rates exceeding 40% in several studies. In randomized clinical trials, the activity of docetaxel exceeds that of doxorubicin, previously considered to be the most effective drug against breast cancer.\[37\] It is, therefore, imperative to evaluate the contribution of this drug to adjuvant chemotherapy and to determine the optimal way to incorporate it into standard therapy for primary breast cancer. Below is a review of the potential strategies to incorporate docetaxel into adjuvant chemotherapy of breast cancer.

Sequential Combination With Anthracycline-Based Regimens

The simplest strategy is to add several cycles of single-agent docetaxel after completing the planned anthracycline-containing regimen. This design is similar to that used by CALGB 9344 and NSABP B-28 to determine the efficacy of paclitaxel in adjuvant treatment.\[38\] The French Cooperative Group uses the same design but compares the same number of chemotherapy cycles (six vs six) rather than a different number of chemotherapy cycles (eg, four vs eight) (Table 1). The Eastern Cooperative Oncology Group (ECOG) trial E1199 also uses this approach but compares taxane-containing arms without a control arm.

Currently, there are two competing hypotheses about drug combinations being tested both in metastatic and primary breast cancer. The first, with over 30 years of experience to support it, is based on the Goldie-Coldman hypothesis and the earlier work of Skipper and Schabel.\[39-42\] It calls...
for the simultaneous administration of two or more drugs at the maximum tolerated doses for the combination. The second, based on the Norton-Simon hypothesis, calls for the sequential administration of single-agent therapy, also at the maximum tolerated doses.[43,44] This second hypothesis was developed at the time when it was believed that dose and dose-intensity were major determinants of outcome, and, therefore, the administration of each cytotoxic drug at the maximum tolerated single-agent dose was of the utmost importance.[45,46] Clinical trials performed over the past decade have suggested that dose and dose intensification are not major determinants of outcome for the most important drugs in the treatment of breast cancer (taxanes, anthracyclines, alkylating agents).[32,47-49] Therefore, continued testing of these two hypotheses may provide information primarily related to quality of life, rather than leading to improvements in outcome.

Some of the trial designs call for single-agent docetaxel to be administered sequentially before or after other commonly used cytotoxic agents (doxorubicin, epirubicin, cyclophosphamide). Regardless of the hypothesis being followed, it is likely that all regimens in which single-agent docetaxel is added sequentially to other drugs or drug combinations will result in similar outcomes. The conglomeration of these studies will define whether the addition of docetaxel to "standard" adjuvant chemotherapy provides an improvement in relapse-free and overall survival rates.

**Simultaneous Combinations With Anthracycline-Based Regimens**

Another approach to incorporating a new drug into the management of primary breast cancer is to add it to existing regimens. This approach is based on the assumption that the new drug is independently effective against the tumor being treated, that it lacks complete cross-resistance with the other drugs included in the combination, and that the toxicities of the new and old agents are not completely overlapping. Since existing drugs given in combination already employ the maximum tolerated doses of each drug in the combination, it is likely that the addition of another drug (in this case, docetaxel) will require a modest reduction in doses for the "standard" drugs as well as for the "new" drug.

The NSABP B-30 and Breast Cancer International Research Group (BCIRG) 005 trials are protocol designs representative of this approach. These clinical trials will determine whether the addition of a third drug will improve the therapeutic effect of the combination sufficiently to exceed the probable decrease in efficacy because of necessary dose reductions, and whether the improved efficacy will compensate for increases in toxicity. Should this strategy be successful, it would lead to the development of shorter and more effective regimens than the previously described strategy; the sequential addition of docetaxel, on the other hand, would lead, by force, to the prolongation of adjuvant chemotherapy programs.

**Substitution for Another Drug in an Established Chemotherapy Regimen**

A third conceptual approach to incorporating docetaxel in adjuvant chemotherapy of breast cancer is to take an existing combination, remove one of the drugs, and incorporate docetaxel instead. The advantage of this approach is that, in general, no dose reductions for the remaining components of the original combination are needed. However, this approach assumes that docetaxel is more effective than the drug being dropped from the original combination and thus will improve the efficacy of the regimen. Representative clinical trials exploring this strategy are included in the bottom section of **Table 1**. Of note, the NSABP B-30 protocol compares all three strategies for introducing docetaxel into adjuvant therapy (**Figure 1**). While this three-arm trial will determine whether any of the approaches is superior to the others, there is no "control" arm (ie, a treatment arm without docetaxel).

The results of the planned interim analysis of the BCIRG 001 trial comparing TAC (docetaxel [Taxotere], doxorubicin [Adriamycin], cyclophosphamide) with FAC are available (**Figure 2**).[50] At 33 months, TAC showed an overall improvement in disease-free survival (32% risk reduction, \(P = .001\), log-rank analysis), the study's primary end point. A 29% reduction in mortality was also observed (\(P = .049\), multivariate COX analysis). A prospective analysis by nodal status revealed a 50% reduction in relapse rate (\(P = .0002\)) and a 54% reduction in mortality rate (\(P = .0006\)) in patients with one to three positive nodes. Additional follow-up will confirm these results and the appropriate integration of TAC in the adjuvant setting.

Whereas docetaxel was shown to be superior to doxorubicin in a phase III trial and, by inference, is considered to be one of the most effective agents against breast cancer, there is limited information about its comparative efficacy in relation to other commonly used anticancer agents. This third strategy is particularly attractive in the specific situation of patients with HER2/neu-overexpressing breast cancers, however.[51]

Our increased understanding of the biology of breast cancer led to the development of a specific
intervention for the treatment of HER2/neu-overexpressing breast cancers.[52,53] Trastuzumab [Herceptin], the monoclonal antibody that binds with a high degree of affinity to the extracellular domain of the Her2 oncoprotein and thus interferes with HER2 signaling, has been shown to have substantial antitumor activity in HER2/neu-positive tumors.[54] When added to cytotoxic therapy, it improves response rate, time to progression, and survival.[55,56] However, trastuzumab in combination with doxorubicin leads to cardiac toxicity in 27% of patients, including an almost 10% incidence of congestive heart failure.[55] Thus, although randomized trials indicated that anthracycline-containing regimens are the most effective cytotoxic treatment for primary breast cancer, there is intense interest in developing non-anthracycline-containing regimens for patients with HER2/neu-positive tumors.[57] Such a combination would reduce the risk of cardiac toxicity to a minimum.[38]

The absence of an anthracycline in the adjuvant therapy of HER2/neu-overexpressing tumors is problematic, however, since several retrospective analyses suggest that anthracyclines are clearly an important component of the treatment of patients with HER2/neu-positive tumors.[58-63] This strong belief in the need to use anthracyclines for the treatment of HER2/neu-positive tumors is also reflected in the fact that the only trial to date that includes a non-anthracycline-containing arm in the adjuvant therapy of HER2/neu-positive tumors is BCIRG 006 (Figure 3). The BCIRG 006 trial design will test the nonanthracycline regimen of docetaxel, carboplatin [Paraplatin]), and trastuzumab, a combination that demonstrated a synergistic interaction in breast cancer modeling studies.[64] All remaining completed or ongoing trials attempt to minimize the risk of cardiac toxicity by avoiding the simultaneous administration of the anthracycline and trastuzumab, by using a less cardiotoxic anthracycline (liposomal anthracyclines or epirubicin), or by adding a cardioprotector agent such as dexrazoxane (Zinecard) to the combination.

Conclusions

The development of docetaxel was a major contribution to our therapeutic armamentarium. Currently, multiple clinical trials are recruiting patients to assess the contribution of this active drug to the curative management of this disease. The inclusion of taxanes, newer hormonal therapies, trastuzumab, bisphosphonates, and other, biologically based interventions is expected to further improve the prognosis of patients with breast cancer. Clinical research in this area should continue, grounded in sound biological principles, optimal trial methodology, and enhanced participation by physicians and patients alike. Our markedly expanded understanding of the biology of breast cancer, along with the development of novel targets and corresponding therapeutic agents, provides us with enhanced opportunities for improved results.

References:


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