Adjuvant Drug Treatment for Resectable Breast Cancer

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ABSTRACT

Breast cancer is the most common life-threatening malignancy in Western women and the second most common cause of cancer-related death. A paradox in the care of patients with breast cancer is the observation that the majority appear to be curable at the time of initial surgery, yet a large number later experience relapse followed by death from disease. To combat this problem, systemic drug therapy in conjunction with surgery and radiation therapy is now standard for many patient subgroups. Standard medical treatment options include up to five years of tamoxifen for receptor positive amenorrheic patients, approximately six months of combination chemotherapy for younger patients and those who are receptor negative, and both in some patient subgroups. These interventions have a profound public health impact even though the majority of patients destined to recur do so even following “optimal” treatment. Further improvements are hoped for as a result of ongoing research involving the use of high-dose chemotherapy, dose-dense chemotherapy, and newer agents. Clinical trials testing these approaches offer the best chance to continue our progress and help to better define appropriate and standard treatment strategies for the future. The Oncologist 1997;2:351-358.

INTRODUCTION

In the developed world, most breast cancer is diagnosed when resectable. Despite this, a large minority of patients experience relapse, making this disease the second most common cause of cancer-related death [1].

Modern treatment for breast cancer is multidisciplinary and includes surgery, radiation therapy, and medical therapy. At the beginning of the 20th century, it was hypothesized that breast cancer spread in an orderly fashion by direct extension into contiguous tissues and then via lymphatic circulation to the rest of the body [2, 3]. As a consequence, total resection of the cancer and the immediate lymphatic drainage was predicted to be curative. Halsted, acting on this belief, treated a series of patients with radical mastectomy and demonstrated improved outcomes [3]. However, the fact that patients treated surgically still develop recurrence makes this model incomplete. To explain this observation, an alternative hypothesis was developed which predicts that unrecognized micrometastatic disease exists at or before the time of primary surgery. Because this reasoning suggests that only effective systemic therapy can offer improved outcomes compared to any surgical approach, it has had a profound influence on treatment approaches over the past several decades [4].

A BRIEF HISTORY OF ADJUVANT THERAPY

Oophorectomy was both the first effective systemic therapy and the first effective adjuvant therapy for breast cancer, and this treatment served as the “proof of principle” that adjuvant therapy could be effective [5, 6]. The impact of oophorectomy is modest, however, and its applicability limited to premenopausal patients [7]. In addition, its long-term health effects, such as premature menopause, are worrisome, particularly as we encounter more and more young patients with mammographically detected low-risk tumors; hence, it remains relatively unpopular as a routine treatment. At the same time, randomized clinical trials continue to test this intervention either alone or in addition to chemotherapy and/or other hormone manipulations such as tamoxifen.

Following the initial demonstration that oophorectomy could be effective, more than one hundred individual prospective randomized adjuvant therapy trials and many hundreds of nonrandomized ones have been conducted. These trials examined hormonal manipulations, chemotherapy, other interventions (i.e., diet, immunomodulation, or others) or combinations of these approaches. Accurate interpretation of this large and growing body of data is difficult because many of these trials have been reported several times, either while

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they were still being conducted or afterward; the treatment effect is usually modest; and many studies are relatively small. Further, multiple analyses and replications of experiments will frequently produce some “positive” and some “negative” findings merely by random chance. Hence, we badly need a mechanism for placing these many studies in perspective so that we can inform both investigational and non-research treatment strategies.

THE EARLY BREAST CANCER TRIALISTS’ COLLABORATIVE GROUP
To answer this challenge, a series of meta-analyses have been performed at five-year intervals by The Early Breast Cancer Trialists’ Collaborative Group. Beginning in 1985, this group has examined in overview all mature and properly randomized trials performed anywhere in the world having at least five years’ follow-up that are concerned with the care of early-stage breast cancer [8]. At the 1990 meeting, 10 years of follow-up were available for many studies and the 15 years were available at the soon-to-be reported 1995 meeting. Because the overview process and its strengths and weaknesses have been extensively reviewed elsewhere, we will instead focus only on its conclusions [9, 10]. In addition, because the results of the 1995 meeting remain largely unpublished and because longer follow-up is unlikely to dramatically change the previously reported results, we will continue to use the 1990 overview for clinical guidance.

The overall conclusions of the overview are at once reassuring and provocative. In summary, treatment provides a consistent and persistent benefit in all risk groups. Indeed, the benefits of therapy continue to increase long after treatment has ceased. We know this because a reduction in the annual risk of recurrence is observed every single year for at least 10 years of follow-up. At the same time, not all patients benefit equally. In general, chemotherapy works best in the youngest patient groups, while hormone therapy (tamoxifen) as predicted, works best in receptor-positive post-menopausal patients. However, within these subgroups, higher- and lower-risk patients, defined pathologically by nodal status, do benefit to the same relative degree. The absolute impact is, however, greater in those with higher risk. By way of illustration, consider the effect of treatment on a high-risk group as compared to a low-risk one. If treatment reduces the annual odds of an event by one-third in all cases, the high-risk population, with a 15% annual risk, has its 20% chance of being disease-free after 10 years (without systemic treatment) improved to 35% because treatment changes the yearly risk to 10%. The same therapy and therapeutic effect (one-third reduction in annual odds of recurrence) in a lower-risk group with a 1.5% annual risk lowers the annual risk to 10% and the overall risk of recurrence at 10 years from 14% to 10% [11]. Hence, a consistent relative impact translates into a larger absolute benefit in higher-risk patients.

These estimations allow us to make educated guesses as to the impact of therapy in various groups, but they do not necessarily describe the precise impact of any specific treatment regimen. This is because the meta-analysis is a form of homogenization where similar, but not necessarily identical, studies are grouped together for analysis and cannot supplant the examination of individual trials asking narrow questions with regard to treatment in selected subgroups. Moreover, to assure adequate follow-up, the methodology excludes newer trials which we hope are testing more active regimens. An additional challenge to the meta-analysis technique arises because newer trials appropriately use some form of effective conventional therapy as control arms, but this blunts the apparent effect of the experimental one. This is in contrast to most of the trials included in earlier meta-analysis where the control arms were untreated and the differences between the arms likely to be greater, allowing for easier detection of treatment effects. As we look beyond the 1995 analysis, we may need to consider only the largest of the studies (several current Intergroup trials exceed 3,000 randomized patients), and we may still be unable to adequately place the impact of the most innovative programs because they may be so unique that they are not easily grouped with other studies. Finally, and adding even more complexity, is the possibility that large, or even small, differences in the agents employed, doses, and schedules, and precise methods of follow-up and evaluation are not reflected in the overview. For all of these reasons, accurate interpretation of this area of research must continue to incorporate not only the overview but also the results of individual trials. At the same time, the overview is a powerful means of answering the most basic questions concerning the use of adjuvant therapy. These include whether or not chemotherapy and/or hormone therapy work in general, and if so, to what extent and in which patients.

TAMOXIFEN IN THE OVERVIEW
The largest single group of patients in the overview is available to address the effectiveness of tamoxifen. More than 30,000 patients were included in these studies, demonstrating
In addition to preventing systemic relapse, there are other potential benefits associated with tamoxifen use. Because of its estrogen-like effects, it may reduce the rate of progression of osteopenia in postmenopausal women, although a potentially deleterious effect on bone density has been suggested for premenopausal women [22-24]. Tamoxifen alters lipid profiles in a favorable direction and may reduce the risk of coronary artery disease. Several adjuvant therapy trials suggest a protective effect against second primary breast cancers, and a large randomized trial conducted by the NSABP has been completed aimed at demonstrating this effect in women with no prior history of the disease. These benefits are not yet certain enough to justify the use of tamoxifen independent of its benefits in terms of prevention of recurrence, although we look forward to the results of the NSABP trial, in particular. At the same time, clinicians should remain alert for the results of ongoing trials of selective ER modulators which may offer similar or greater benefits with less toxicity.

**Chemotherapy in the Overview**

The overview showed that chemotherapy lowers the annual odds of recurrence by 28%, with an absolute benefit of 8.4% at 10 years of follow-up. A 16% reduction in the annual risk of death was seen, resulting in 6.3% fewer deaths overall after 10 years [8]. Chemotherapy combinations were superior to single agents, and CMF (cyclophosphamide, methotrexate, and 5-fluorouracil) was the chemotherapy regimen most well represented. Additional drugs beyond CMF did not appear to improve outcomes, and two “standard” versions of CMF (all i.v. at 21-day intervals or day 1 and 8 i.v. treatment with methotrexate and 5-fluorouracil with oral cyclophosphamide on days 1 through 14) are most widely used, in either case for about six months. Longer durations of therapy have not been shown to be better, and a single cycle of treatment is inferior [25, 26]. Dose reductions to minimize toxicity may compromise effectiveness when 85% or less of the planned dose intensity is delivered [27]. The omission of cyclophosphamide compromises efficacy, particularly in younger patients [28, 29].

**Other Chemotherapy Combinations**

The discovery of additional drugs with activity against metastatic breast cancer motivates their use as adjuvant treatment. As noted above, the addition of most drugs to CMF does not consistently improve the outcome. One exception to this observation may be doxorubicin. A review of numerous trials shows that the combination AC or CAF is usually equivalent to CMF, with some higher-risk subsets of patients sometimes appearing to benefit from the addition of anthracycline [30-33]. The reasons for our failure to consistently demonstrate a significant benefit when...
using doxorubicin may include the low risk of most tested patient groups or our suboptimal dosing for this agent. The latter point has been addressed in an elegant study from Milan in which patients were treated with non-cross-resistant chemotherapy consisting of single-agent doxorubicin and the combination CMF [34]. Half of these high-risk patients with four or more involved axillary nodes received alternating therapy with two cycles of CMF for every dose of doxorubicin while the other half received the same total doses of drugs given as four cycles of doxorubicin, first followed by all eight doses of CMF (A \rightarrow CMF). The fascinating result of this experiment, consistent with preclinical models, was that sequential therapy was superior even when all patients received the same size doses, the same doses, and the same total time of treatment [35-37]. Based on this trial, many clinicians favor this sequential regimen for higher-risk node-positive patients, and this success has influenced a subsequent crop of clinical trials, including many incorporating taxanes, to be discussed below.

**Tamoxifen Plus Chemotherapy**

The benefits of tamoxifen and chemotherapy are easiest to determine in comparison to wholly untreated control populations. However, the question of chemotherapy and tamoxifen together is answerable only through trials comparing one treatment modality with both.

The overview shows that tamoxifen adds to the benefits of chemotherapy, and vice versa, particularly in postmenopausal patients [8, 10]. For women aged 50 or above, indirect estimations of the treatment effect show that tamoxifen added to chemotherapy yields an additional 28% reduction in the yearly odds of recurrence over and above the 22% reduction already gained from the use of combination chemotherapy. Certainly, tamoxifen remains the gold standard for postmenopausal receptor-positive patients, in part because it is considerably less toxic than chemotherapy. Yet, it is also reasonable to treat patients who have considerable risk of recurrence with both modalities to optimally reduce their absolute risks of recurrence and death. Several recent reports of chemotherapy plus tamoxifen support this approach, and a major controversy now concerns the issue of which patient groups can forego chemotherapy [38-41]. When both are used, whether the chemotherapy and tamoxifen should be delivered concurrently or sequentially is also unresolved. Concurrent therapy may increase the risk of acute toxicities without increasing effectiveness, but a now-completed randomized trial testing chemotherapy with, or followed by, tamoxifen will help resolve this issue [40].

**Risk Assessment and the Choice of Adjuvant Therapy**

As described earlier, there is a linkage between the risk of recurrence or death and the absolute size of the benefit demonstrated in the overview. This means that an accurate risk assessment is required to guide treatment decisions, because even though low-risk patients benefit to the same proportional degree as higher-risk patients, at some point the absolute size of this benefit is too small to outweigh the potential risks of treatment itself.

Sequential therapy was superior even when all patients received the same size doses, the same total doses, and the same total time of treatment.

**Ipsilateral axillary lymph node involvement** is the most reproducible estimator of risk [42, 43]. The growing enthusiasm for sentinel node biopsy to determine whether or not there is nodal positivity (and whether or not the surgeon should proceed to a full axillary dissection).

Tumor size remains the most consistent and reliable prognostic factor for node-negative patients [44]. Infiltrating ductal carcinomas, not otherwise specified, or infiltrating lobular carcinomas measuring up to one centimeter in diameter have a 13% actuarial risk of relapse at 21 years, while special histologic types of node-negative cancer such as tubular, papillary, true medullary, mucinous, or adenoid cystic have a similarly low risk of recurrence with tumor diameters of up to three centimeters. Patients with tumors in these lowest-risk categories might gain no more than two percentage points in benefit distributed over ten years from systemic therapy. Because this predicted benefit is so small, and because there are not yet any properly randomized data for this subgroup, treatment is not standard in this setting. Treatment should be considered for all patients with higher risk based on either nodal positivity or tumor size [45]. The role of other prognostic factors remains to be established.

**The Timing of Radiotherapy and Surgery in Relationship to Chemotherapy**

The most advantageous means of sequencing surgery, radiation therapy, and systemic therapy are uncertain and are the subject of ongoing clinical trials. Because chemotherapy successfully shrinks locally advanced breast cancers and can allow local-control surgery in the majority of cases, there has
been enthusiasm for broader use of neoadjuvant therapy. Neoadjuvant therapy has been shown to allow more breast conservation in patients with initially resectable disease, but this earlier use of chemotherapy does not influence the risk of relapse or death [46, 47]. Based on these data, neoadjuvant chemotherapy could be most reasonable for patients who refuse to undergo mastectomy but for whom a limited excision and radiation therapy would be acceptable. On the other hand, it is possible that the risks of over-treatment (i.e., chemotherapy given for largely in situ carcinomas) for low-risk patients could outweigh the benefits of this approach. Hence, outside of clinical trials, most patients with resectable breast cancer should undergo definitive surgery for local control and staging before beginning systemic treatment.

Following surgery, the timing of systemic therapy and radiotherapy is also an issue. The early use of radiotherapy minimizes the risk of local recurrence in patients treated with breast conservation but may compromise the delivery of chemotherapy, which, in turn, could increase the risks of distant relapse and death [48-51]. A modestly sized randomized trial comparing radiation first versus radiotherapy following chemotherapy was consistent with these predictions; early radiotherapy lowered the incidence of local recurrence but increased the incidence of life-threatening systemic recurrence, particularly in patients with positive axillary lymph nodes [52]. At present, for most patients with operable breast cancer, an appropriate sequence of treatments is to first undergo definitive surgery (if feasible), then chemotherapy (if indicated), followed last by radiotherapy (if indicated). Tamoxifen can start during or following radiotherapy with no apparent differences in these two approaches.

**FUTURE DIRECTIONS**

That there is a relationship between dose and cell-kill seems intuitive, but laboratory demonstration of such a relationship for selected drugs (particularly alkylating agents) in tumor lines motivated the testing of higher doses in humans [53]. Within “standard” dose ranges, both retrospective and prospective randomized adjuvant therapy trials show that dose size and also dose intensity are important in prolonging disease-free survival [54, 55]. This, along with numerous breakthroughs in supportive care, such as the availability of growth factors and autologous stem cell harvesting and infusion, has motivated the testing of even higher doses. The worth of this promising approach will be defined by the two large randomized cooperative group studies in patients with 10 or more involved lymph nodes which are expected to complete accrual shortly [56, 57].

Yet, even when completed, these trials will leave questions unanswered with regard to high-dose treatment. For example, what is the most appropriate timing of high-dose therapy? Is a single cycle of high dose treatment enough? An intriguing trial from Duke University suggests that “early” treatment (i.e., immediately following induction to maximal response) may be, contrary to earlier predictions, inferior [58]. Patients receiving high-dose treatment delayed until the time of disease progression not only responded well, with many re-entering complete remission, but also survived on average more than one year longer than those receiving immediate very high-dose chemotherapy. An extrapolation to high-risk early-stage disease suggests the possibility that withholding high-dose treatment until the time of first recurrence could possibly be superior to the current strategy of following induction therapy with immediate high-dose consolidation.

At the same time, we must consider emerging evidence suggesting the existence of a plateau in the dose-response relationship for some agents, such as cyclophosphamide. Specifically, the NSABP trials B-22 and B-25, which tested a fourfold increase in cyclophosphamide dose and dose intensity, are thus far negative and clearly demonstrate increased toxicity for the higher doses [59]. Subsequent NSABP trials B-27 and B-28 have returned to “standard” AC (i.e., doxorubicin 60 mg/m² and cyclophosphamide 600 mg/m²). Whether or not we have reached plateau in the dose-response relationship, most models predict that multiple, not single, cycles of chemotherapy will be necessary to eradicate sensitive clones, and conventional chemotherapy by and large adheres to this hypothesis.

**DOSE DENSITY**

Based on this assumption, a strategy which can be additive or alternative to dose escalation concerns the use of dose-dense treatment plans. These are based on earlier laboratory and mathematical models of tumor growth and response to treatment predicting the need for multiple, rather than single, cycles of therapy [60]. The goal of this approach is to deliver these multiple cycles of optimally dosed chemotherapy using the shortest possible intertreatment intervals. The appellation “dose-dense” distinguishes this approach from the previous trials of dose-escalation. The trial comparing more dose-dense sequential therapy (four cycles of doxorubicin followed by eight more cycles of CMF, A → CMF) to a less dose-dense alternating plan discussed above serves as proof of principle for this concept and has led to several follow-up studies [61].

In one pilot trial, high-dose cyclophosphamide was given using a dose-dense, every-two-week treatment interval for three cycles in place of the CMF used in the earlier sequential A → CMF regimen [62]. Based on this study, A → C was compared against concurrent AC in a Southwestern Oncology Group (SWOG)-led Intergroup trial open to women with high-risk node-negative disease or up to three involved axillary...
lymph nodes. As of May 1997, accrual has been completed, but the results are not yet available.

Another way of improving adjuvant therapy is through the addition of new active non-cross-resistant agents. In this regard, the taxanes, which currently include paclitaxel and docetaxel, have emerged as most promising in recent clinical trials in metastatic breast cancer [63-66]. However, the best means of incorporating these agents is not yet known. Phase II trials testing the simultaneous combination of paclitaxel and doxorubicin demonstrated provocative activity but also unexpected toxicity [67, 68]. Further, a large multicenter randomized trial conducted by the ECOG comparing single-agent doxorubicin versus paclitaxel versus the combination suggested far more modest results for this combination, although the dose and schedule of administration were somewhat different in comparison to the earlier phase II studies [69]. Based on this activity, a European three-arm multicenter trial compares doxorubicin versus doxorubicin plus paclitaxel, with CMF following in either case, based on the earlier trial of A → CMF. The third arm of this trial delivers all the chemotherapy as neoadjuvant therapy. Most other trials are using paclitaxel or docetaxel separately as single agents administered subsequent to standard therapy, usually AC, and some of these trials are already completed or nearly so. Presently, results are anxiously awaited from the Cancer and Leukemia Group B (CALGB 9344)/Intergroup trial of four cycles of AC with or without four more cycles of paclitaxel and from a very similar NSABP trial (B-28).

A dose dense treatment plan incorporating doxorubicin, paclitaxel, and cyclophosphamide has been tested with promising results. Building on the earlier study of A → C, three cycles of doxorubicin are followed by three of paclitaxel and then three of cyclophosphamide, and doses are escalated above the standard levels with each cycle supported by G-CSF. Intertreatment intervals are two weeks for all nine cycles of therapy [70, 71]. Because the early results were extremely promising, this regimen is now being compared in several randomized studies against other more or less conventional approaches. For postoperative patients with four to nine positive nodes, this regimen is compared against doxorubicin and cyclophosphamide followed by high-dose chemotherapy, while another adjuvant study will use a variation on this regimen in lower risk patients and compare two versus three-week treatment intervals while also comparing A → T → C against the more “conventional” AC → T.

**CONCLUSION**

Early detection and improved therapy together have reduced the mortality for breast cancer in the United States [1]. Systemic drug therapy in conjunction with surgery and radiation therapy is now standard for many patient subgroups although the specific decision to use hormonal therapy (five years of tamoxifen), four to nine months of combination chemotherapy (AC, CMF, CAF, or other treatment plans), or both remains complex and controversial. Dose-escalated treatments along with more dose-dense plans, as well as regimens incorporating newer agents are promising, but remain investigational. Patient and physician participation in current clinical trials offer the best chance to continue our progress and help to better define appropriate treatment strategies.

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