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REVIEW ARTICLE

Chemotherapy: What Progress in the Last 5 Years?

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INTRODUCTION

It is 1999, during the American Society of Clinical Oncology (ASCO) Annual Meeting, and the plenary session is dedicated to the randomized studies that have failed to demonstrate a meaningful benefit from high-dose therapy in breast cancer. The aromatase inhibitors are showing real promise, though. They have already become the agents of choice in postmenopausal women with estrogen receptor (ER) –positive metastatic disease after tamoxifen failure, and are challenging tamoxifen as the gold standard in metastatic disease. Trastuzumab is US Food and Drug Administration (FDA) –approved as a single agent in HER-2 overexpressed metastatic disease, and an indication for combination therapy is imminent. Pamidronate has just been registered for bone metastases. Docetaxel is now the reference cytotoxic in metastatic disease, but paclitaxel and capecitabine also have US FDA indications in this setting. Although lacking a US FDA indication in breast cancer, vinorelbine (registered for non–small-cell lung cancer), gemcitabine (registered for pancreatic cancer and non–small-cell lung cancer), pegylated liposomal doxorubicin (registered for Kaposi's sarcoma and submitted for ovarian cancer), and mitoxantrone (registered for hormone-refractory prostate cancer and acute nonlymphocytic leukemia) are also in use in third-, fourth-, and fifth-line therapy. In the adjuvant setting, doxorubicin and cyclophosphamide are the mainstay of current adjuvant regimens, paclitaxel has just received an accelerated approval for use after standard doxorubicin-containing therapy and, after years of use in the rest of the world, epirubicin has finally hit the US market.

Since 1999, though, fulvestrant and zoledronic acid are the only new agents to be US FDA–approved for breast cancer therapy (http://www.fda.gov). The relative lack of new drug registrations does not reflect a lack of progress, however. The turn of the century marked the start of a profound shift in attitude regarding management of metastatic disease. Improvements in both efficacy and tolerability of systemic therapy have been achieved by modifying drug formulation and/or dose schedule; liposomal encapsulation can modify both the pharmacokinetics and tissue distribution of active agents, oral formulations permit continuous exposure of the tumor to the cytotoxic, tumor-specific enzymes can be harnessed to selectively activate prodrugs in order to spare normal tissues from toxicity, and the traditional 3-weekly dosing schedule is now the exception rather than the rule.

SINGLE AGENTS IN METASTATIC BREAST CANCER

Antitubulins

Docetaxel. By 1999, docetaxel had become the reference agent in metastatic breast cancer, and it remains so in 2004. A randomized trial of 326 patients demonstrated superiority of docetaxel (100 mg/m^2 every 3 weeks) over doxorubicin (75 mg/m^2 every 3 weeks) as single agents in terms of response rate (48% *v* 33%; $P = .008$). Although no survival benefit was evident

(15 *v* 14 months), and the difference in time to progression was not statistically significant (26 *v* 21 weeks),[1] the increasing use of anthracyclines in the adjuvant setting left docetaxel as the agent of choice in the metastatic setting. At the 2003 San Antonio Breast Cancer Symposium (San Antonio, TX), a randomized study comparing docetaxel (100 mg/m^2 every 3 weeks) and paclitaxel (175 mg/m^2 every 3 weeks) further advanced docetaxel's market position in metastatic disease. In the intent-to-treat analysis, docetaxel was statistically superior to paclitaxel in terms of time to progression (5.7 *v* 3.6 months; $P = .0001$) and overall survival (OS; 15.4 *v* 12.7 months; $P = .03$), and there was a trend to superiority in terms of response rate (32% *v* 25%; $P = .10$).[2] While docetaxel is generally well tolerated as a single agent, long-term use is often limited by hematologic tolerance, peripheral neuropathy, fatigue, nail toxicity, and fluid retention.

A randomized phase II study comparing weekly and 3-weekly schedules of docetaxel (n = 83) has demonstrated no difference in response rates (34% *v* 33%). The study demonstrated greater grade 3 and 4 toxicity in the 3-weekly arm. Neutropenia (7% *v* 37%), febrile neutropenia (5% *v* 20%), neurotoxicity (2% *v* 17%), and stomatitis (7% *v* 17%) were all more common with the 3-weekly schedule. Asthenia was similar in the two arms (15% *v* 12%). Of interest, however, is that more patients withdrew from study as a result of toxicity in the weekly schedule (46% *v* 37%). Onycholysis (12%), fatigue (7%), lacrimal duct toxicity (7%), and infection (7%) were the main reasons for withdrawal from the weekly schedule, while neurotoxicity (12%), fatigue (7%), skin toxicity (7%), and edema (5%) were the main reasons for withdrawal from the 3-weekly schedule.[3] Of note, higher doses of dexamethasone to prevent fluid retention are used with the weekly schedule (8 mg × 3 per week; 72 mg over 21 days) compared to the 3-weekly schedule (8 mg bid × 3; 48 mg over 21 days), which may be clinically important, particularly when prolonged administration of docetaxel is warranted.

Paclitaxel. Over the past 5 years, paclitaxel has been utilized with less frequency in the metastatic setting for two reasons: firstly, the use of paclitaxel has increased in the adjuvant setting so that many patients with new metastases have already been exposed to the drug; and secondly, the data supporting the use of docetaxel in the metastatic setting has strengthened. With the 3-weekly schedule, paclitaxel has been unable to demonstrate superiority over either doxorubicin or docetaxel in the first-line metastatic setting. In 331 patients, paclitaxel (200 mg/m^2 every 3 weeks) demonstrated lower response rates than doxorubicin (75 mg/m^2 every 3 weeks) both in the first line setting (25% *v* 41%; $P = .003$), and in the 77 patients who crossed over after disease progression (16% *v* 30%). Paclitaxel demonstrated a shorter progression-free survival (PFS) in first line (3.9 *v* 7.5 months; $P < .001$), but the difference in OS (15.6 *v* 18.3 months) did not achieve statistical significance.[4]

The value of paclitaxel may have been underestimated, however. In Cancer and Leukemia Group B (CALGB) 9840, a direct comparison of weekly and 3-weekly paclitaxel in 585 patients, the weekly schedule (80 mg/m^2 over 1 hour) was clearly superior to the 3-weekly schedule (175 mg/m^2 over 3 hours) in terms of response rate (40% *v* 28%; $P = .017$) and time to progression (9 *v* 5 months; $P = .0008$), and there was a trend in favor of weekly paclitaxel in terms of survival (24 *v* 16 months; $P = .17$). Weekly paclitaxel was associated with less hematologic toxicity but more neurotoxicity than the 3-weekly regimen. The statistical validity of the study is unfortunately compromised by the inclusion in the 3-weekly arm of 158 patients who received paclitaxel at 175 mg/m^2 in CALGB 9342, a study comparing three doses of single-agent paclitaxel,[5] but the results nevertheless call into doubt the apparent inferiority of paclitaxel in phase III metastatic studies.[6]

Vinorelbine. Vinorelbine has been the subject of multiple phase II studies in metastatic breast cancer, and is associated with response rates varying from 35% to 50%.[7-15] In a randomized trial, vinorelbine was superior to melphalan in time-to-treatment failure (12 *v* 8 weeks; $P < .001$) and OS (35 *v* 31 weeks; $P = .034$).[16] As a single agent, vinorelbine is extremely well tolerated, and is well suited to elderly patients.[14] The most common toxicities with vinorelbine are neutropenia, gastrointestinal toxicities, and peripheral neuropathy. Alopecia is a rare event. Vinorelbine is associated with phlebitis if administered through a peripheral line.

An oral formulation of vinorelbine is now in development. A phase II study of oral vinorelbine at weekly doses of 60 to 80 mg/m^2 in 64 patients demonstrated a response rate of 31%, with a mean delivered dose intensity of 63 mg/m^2 per week.[17]

Anthracyclines

Doxorubicin and epirubicin. Doxorubicin (60 mg/m^2 every 3 weeks) or epirubicin (100 mg/m^2 every 3 weeks) are the cornerstone of most adjuvant breast cancer regimens, and were the reference agents in metastatic breast cancer until they were unseated by docetaxel in the late 1990s. They retain significant activity (response rates, 30% to 40%) in women who are anthracycline-naïve or who develop metastases more than 12 months after receiving anthracyclines in the adjuvant setting,[1,4] but their efficacy in women who have an anthracycline-free interval of less than 12 months is uncertain. Their use in the metastatic setting is limited by significant acute toxicity (nausea and vomiting, myelotoxicity, alopecia), long-term concerns regarding leukemogenic potential, and cardiotoxicity

occurring at cumulative doses above 450 mg/m^2 of doxorubicin (8 cycles over 24 weeks), or 1,000 mg/m^2 of epirubicin (10 cycles over 30 weeks).

Pegylated liposomal doxorubicin. Pegylated liposomal doxorubicin (PLD) has a longer half-life than free doxorubicin (2 to 3 days *v* <10 minutes), and accumulates preferentially in malignant tissue.[18] Following a study that demonstrated comparable efficacy to doxorubicin with a much better toxicity profile, this agent is gaining popularity in the metastatic setting. The trial compared PLD (50 mg/m^2 every 4 weeks) to free doxorubicin (60 mg/m^2 every 3 weeks). With 509 patients randomly assigned, there was no difference in outcome in terms of response rate (33% *v* 38%), PFS (6.9 *v* 7.8 months), or OS (21 *v* 22 months). The toxicity profiles of the two formulations were quite distinct, however. PLD was associated with less gastrointestinal side effects (nausea, 37% *v* 53%; vomiting, 19% *v* 31%), less alopecia (20% *v* 66%), less myelotoxicity (neutropenia, 4% *v* 10%) and less cardiotoxicity (3.9% *v* 18.8%; hazard ratio, 3.16; $P < .001$) than free doxorubicin. Skin toxicity (plantar-palmar erythrodysesthesia) and mucositis were more common with the liposomal formulation (48% *v* 2% and 23% *v* 13%, respectively). PLD was also associated with hypersensitivity reactions in a minority (13%) of patients.[19] PLD has been studied in schedules ranging from 20 mg/m^2 every 2 weeks to 60 mg/m^2 every 6 weeks,[19-21] and cardiac toxicity has been reviewed in patients who have received cumulative doses of PLD exceeding 500 mg/m^2 (10 cycles over 40 weeks). In 42 patients, there were five left ventricular ejection fraction–defined cardiac events, and no cases of congestive cardiac failure.[22] The skin and mucosal toxicities of PLD are clearly schedule-dependent; mucositis is more common in those schedules with higher total dose per cycle (45 mg/m^2), while plantar palmar dysesthesia is more common when the dose intensity is increased (>10 mg/m^2 per week). These toxicities can therefore usually be effectively managed by reducing the total dose per cycle or by prolonging the treatment interval in affected patients.

TLC D-99 (Myocet). As yet lacking a US FDA indication, TLC D-99 is commercially available in Europe. TLC D-99 is distinct from PLD in terms of its liposome formulation; the D-99 liposome is larger than the PLD liposome, has a half-life closer to that of free doxorubicin, and is susceptible to uptake by the reticuloendothelial system.[23] TLC D-99 is provided as a three-vial system (doxorubicin, liposomes, buffer) that must be prepared on site using a method that involves heating the doxorubicin. The dose of TLC D-99 used is equivalent to that of the free agent. Like PLD, TLC D-99 has been compared with free doxorubicin in a randomized trial. The study compared TLC D-99 (75 mg/m^2 every 3 weeks) with doxorubicin (75 mg/m^2 every 3 weeks) in 224 patients with metastatic breast cancer. There were no significant differences between the TLC D-99 and doxorubicin groups in terms of response rate (26% *v* 26%), time to progression (2.9 *v* 3.1 months), or OS (16 *v* 20 months; $P = .09$). Cardiac toxicity (13% *v* 29%) was less in the TLC D-99 arm, and the median onset of cardiac toxicity occurred later (median cumulative dose, 785 *v* 570 mg/m^2) than with free doxorubicin. Skin toxicity was a rare event.[24] Although indirect comparisons have obvious weaknesses, these data suggest that the two liposomal agents have comparable efficacy. The logistics of preparation of TLC D-99, and its lack of US FDA registration have, however, restricted its use in the United States.

Fluoropyrimidines

Capecitabine. Capecitabine is a prodrug of fluorouracil (FU) that requires three enzymatic steps for activation. The final step of this activation pathway involves thymidine phosphorylase, an enzyme that is overexpressed in malignant tissues, theoretically protecting normal tissues from exposure to the active drug. Capecitabine offers the efficacy of infusional FU without the inconvenience of drug pumps and venous access devices. Administered orally for 14 days in a 3-weekly cycle, it was US FDA–registered when it demonstrated a 20% response rate in breast cancer patients with paclitaxel-refractory disease.[25] While no direct comparisons of capecitabine and infusional FU have been published, randomized studies between capecitabine and bolus FU in patients with colorectal cancer have demonstrated less diarrhea, stomatitis, nausea, alopecia, and neutropenia, and more hand-foot syndrome and hyperbilirubinemia with the oral agent.[26,27] While this may reflect differences between continuous and bolus dosing, rather than between FU and capecitabine, capecitabine is nonetheless well tolerated when patients are educated in the management of potential toxicities. As with infusional FU, care needs to be taken in patients with a history of coronary disease.[28]

Other

Gemcitabine. In phase II studies in metastatic breast cancer, gemcitabine (1,200 mg/m^2 over 30 minutes, days 1, 8, and 15, every 4 weeks) has demonstrated response rates ranging from 14% to 37%.[29-32] This agent has been unable, however, to demonstrate efficacy in patients with prior exposure to anthracycline and taxane; the only single-agent study in this setting demonstrated no objective responses in 23 patients.[33] In the early 1990s, studies in leukemia patients showed that cellular accumulation of triphosphorylated (active) gemcitabine reaches a plateau at plasma concentrations of gemcitabine that exceed 15 μmol/L, achieved clinically by infusion rates of 10 mg/m^2/min.[34] A subsequent randomized phase II study comparing infusional dosing (1,500 mg/m^2 over 150 minutes) to standard dosing (2,200 mg/m^2 over 30 minutes) in patients with pancreatic cancer demonstrated a statistically significant

survival advantage to the infusional schedule (8 month *v* 5 month; $P = .013$).[35] The only trial of infusional gemcitabine in breast cancer used a weekly schedule of 250 mg/m^2 over 6 hours. While this infusion rate is significantly slower than the 10 mg/m^2/min used in the leukemia and pancreatic studies, and is unappealing in terms of the time commitment required by both the patient and chemotherapy staff for administration, a response rate of 25% was observed.[36]

COMBINATION THERAPY IN METASTATIC BREAST CANCER

Combinations That Do Not Contain Trastuzumab

In 2004, one of the most debated issues in the management of metastatic disease is whether combination therapy offers a survival advantage over sequential single-agent therapy. There is little doubt that combination therapy offers higher response rates and longer time to progression. The ability of combination therapy to improve survival over sequential use of the same agents is less clear. The issue is important, as combination therapy is associated with greater toxicity than single-agent therapy. The assessment of response is also less clear when combined therapy has been administered, as response to one agent can mask resistance to another. Conversely, in all areas of oncology where cure is possible for advanced disease, it has been achieved by the use of combination chemotherapy.

To date, no individual trial has demonstrated a convincing survival advantage from combination therapy over the component single agents given in sequence. However, all trials have been underpowered and unable to demonstrate survival differences as high as 20%. A 1998 meta-analysis of 1,986 patients randomly assigned between polychemotherapy and single-agent therapy in the metastatic setting concluded a survival advantage to polychemotherapy, with a hazard ratio of 0.82 (range, 0.75 to 0.90). The individual trials in this meta-analysis were small, however, featured regimens that are no longer in common use, and the use of both prior adjuvant therapy and subsequent lines of therapy for metastatic disease were not reported.[37] In addition, this meta-analysis was based on published material and not individual patient data. Two recently published studies, capecitabine and docetaxel over docetaxel alone, and paclitaxel and gemcitabine over paclitaxel alone, have reopened the debate with claims of statistically significant survival advantages.

Capecitabine/docetaxel. In the capecitabine/docetaxel study, 511 women with measurable metastatic breast cancer who had received a prior anthracycline were randomly assigned to receive either intravenous docetaxel (75 mg/m^2 intravenously [IV] on day 1 every 3 weeks) and oral capecitabine (1,250 mg/m^2 bid on days 1 to 14 every 3 weeks), or intravenous docetaxel (100 mg/m^2 IV on day 1 every 3 weeks). Despite using a lower dose of docetaxel, the combination demonstrated a higher response rate (42% *v* 30%; $P = .006$), longer time to progression (6.1 *v* 4.2 months; $P = .0001$), and longer OS (14.5 *v* 11.5 months; $P = .0126$). The combination therapy was more toxic; 65% of patients in the combination arm had dose reductions compared with 36% in the docetaxel arm. Although there is a preclinical rationale for synergy between capecitabine and docetaxel (docetaxel upregulates thymidine phosphorylase in malignant tissue), the main criticism of the design of this study is the lack of crossover from docetaxel to capecitabine in the single-agent arm. The study was conducted in 16 countries; the availability of capecitabine in those countries at the time the study was conducted is not reported, but only 17% of patients who received single-agent docetaxel received capecitabine off-study after disease progression.[38]

Gemcitabine/paclitaxel. The gemcitabine/paclitaxel study was reported at the ASCO Annual Meeting in 2004.[39] Five hundred twenty-nine women with measurable metastatic breast cancer and prior adjuvant anthracycline but no prior chemotherapy for metastatic disease were randomly assigned to received either paclitaxel (175 mg/m^2 over 3 hours every 3 weeks) and gemcitabine (1,250 mg/m^2 over 30 minutes, on days 1 and 8 every 3 weeks), or paclitaxel alone (175 mg/m^2 over 3 hours on day 1 every 3 weeks). The combination arm reported higher response rates (41% *v* 22%; $P < .0001$), longer time to progression (5.2 *v* 2.9 months; $P < .0001$), and longer survival (18.5 *v* 15.8 months; $P = .018$). The survival differences were based on an interim analysis and do not represent the definitive results of this clinical trial. There was more hematologic toxicity, and more fatigue in the combination arm. The study was conducted in 19 countries; as with the capecitabine/docetaxel study, the availability of gemcitabine in those countries at the time the study was conducted was not reported. Only 14% of patients in the single-agent arm received gemcitabine off-study after disease progression. The greatest cautionary note over the credibility of the survival advantage in this study, however, is that there is no evidence of synergy between these agents at a preclinical level.

Doxorubicin/paclitaxel. The only study that truly compares combination versus sequential therapy is Eastern Cooperative Oncology Group (ECOG) 1193. Seven hundred thirty-nine patients were randomly assigned to receive single-agent doxorubicin (60 mg/m^2), single-agent paclitaxel (175 mg/m^2 over 24 hours), or combination therapy (doxorubicin 50 mg/m^2 and paclitaxel 150 mg/m^2 over 24 hours, with granulocyte colony-stimulating factor [G-CSF] support). Two hundred fifty-seven of the 453 patients initially randomly assigned to single-agent therapy were able to cross over to the alternate agent on disease progression. Response rates in first-line therapy

favored combination therapy; there was no significant difference between doxorubicin and paclitaxel (47% *v* 36% *v* 34%; $P = .007$ for combination *v* doxorubicin). Time to progression also favored the combination (8.0 *v* 5.8 *v* 6.0 months; $P = .009$ for combination *v* doxorubicin). Despite these differences, there were no significant differences between the three arms in terms of survival (22.0 *v* 18.9 *v* 22.2 months) or quality-of-life end points.[40] While this is the largest randomized trial to address this issue, it remains a relatively small study with limited statistical power.

From all available evidence, one can conclude that sequential single-agent therapy is usually less toxic than simultaneous combinations, if similar doses are used. While the survival advantage of combinations over single-agent therapy is controversial, there is no evidence that sequential therapy is superior to combinations. Higher response rates are perceived by some patients as reflecting more effective therapy and are more likely to benefit symptomatic patients; longer time without progression is also favored by some patients. Rational combinations should continue to be explored in an attempt to improve the efficacy of treatment in metastatic breast cancer. Also, exploration of rational combinations in metastatic disease can be helpful for improving treatment of patients with early breast cancer.

Combinations That Contain Trastuzumab

Although trastuzumab is being covered in the first section on targeted therapies of this overview, combinations of chemotherapy with this humanized monoclonal antibody to the HER-2 protein have been broadly adopted. While no randomized studies have yet been performed comparing single-agent trastuzumab to a combination of trastuzumab and chemotherapy, the combination is clearly superior to chemotherapy alone. In addition, preclinical synergy has been demonstrated between trastuzumab and a number of chemotherapeutic agents, most evidently vinorelbine, docetaxel, cyclophosphamide, and carboplatin.[41] Importantly, combinations that have been tested in phase II setting,[42-46] or compared to chemotherapy alone in phase III studies,[47] have also demonstrated significant clinical activity.

PROGRESS IN METASTATIC BREAST CANCER

In 2004, sequential single-agent therapy is frequently used for the management of asymptomatic patients with metastatic breast cancer. For patients with more extensive or symptomatic disease, many oncologists prefer combination therapy. No modern single agent offers a clear survival advantage over any other agent and, with the exception of HER-2 and trastuzumab, no molecular marker has been shown to reliably predict sensitivity or resistance to any individual agent. The choice of agent or regimen is currently made on the history of prior therapy and treatment-free interval, combined with patient preferences regarding route of administration, frequency of treatment, and potential toxicities.

Recent Progress in Chemotherapy of Primary Breast Cancer

The first clinical trial to evaluate the contribution of adjuvant chemotherapy to the management of primary breast cancer started in 1958.[48] However, substantial enthusiasm for adjuvant chemotherapy trials developed only around 1972, based on better understanding of the natural history of human breast cancer and compelling laboratory investigation indicating early dissemination of the disease, often before the initial diagnosis was made.[49] The next three decades led to more than 200 prospective randomized trials of adjuvant systemic therapy, to answer a number of critical questions related to the optimal use of systemic therapy in general, and chemotherapy in particular.

By the end of the 20th century, these studies had demonstrated that adjuvant chemotherapy reproducibly reduced annual odds of recurrence and death for women with primary breast cancer, regardless of age, stage, nodal status, and hormone receptor status. These individual clinical trials were also pooled in the Oxford meta-analysis, and in four consecutive analyses performed every 5 years starting in 1985. The results of individual trials were confirmed and extended, with the added benefit of very large sample sizes providing huge statistical power (the 2000 meta-analysis has been presented in multiple fora, including the 2000 National Institutes of Health Consensus Development Conference, but has not been published in an abstract or full manuscript format).[50-52]

The overview confirmed that combinations of drugs were more effective than single agents, that 4 to 6 months of treatment with the same regimen produced optimal benefit and longer treatment with the same regimen provided no incremental gain, and that for patients with hormone receptor–positive breast cancer, the sequential combination of chemotherapy and endocrine therapy provided additive therapeutic effects.[53] A recent update of a large randomized trial comparing sequential and simultaneous administration of CAF chemotherapy and tamoxifen demonstrated an increase in recurrences with the simultaneous compared to the sequential regimen.[53a] Second generation trials indicated that anthracycline-containing regimens were superior in efficacy to those that lacked anthracyclines, most evidently in three-drug regimens containing an anthracycline, cyclophosphamide, and fluorouracil, usually administered over six to eight cycles.[54,55] Another effective method to incorporate an anthracycline in adjuvant chemotherapy was developed by the Milan group and consists of four cycles of full-dose, single-agent

anthracycline (doxorubicin or epirubicin) followed by four to eight cycles of cyclophosphamide, methotrexate, and fluorouracil (CMF).[56] Within this past year, investigators from the United Kingdom confirmed the superiority of such a regimen over CMF in a randomized trial that included more than 2,000 patients.[57] The last decade of the century also provided over a dozen randomized trials assessing the value of dose escalation and high-dose chemotherapy with autologous hematopoietic stem-cell support in the adjuvant setting.[58] To date, these trials have indicated that while dose reductions below full standard doses were less effective, and should therefore be avoided, dose increases with hematopoietic growth factor support or with stem-cell support did not improve OS, and were associated with substantially higher morbidity and a low but real incidence of treatment-related mortality.

The past 3 to 4 years witnessed another generation of clinical trials providing initial results of new directions in therapeutic research addressing novel chemotherapy-related questions in the management of primary breast cancer. These questions address the following directions in research: (1) the role of taxanes in the adjuvant chemotherapy setting; (2) the comparison of sequential single-agent therapy compared to concurrent therapy; (3) the value of dose-dense administration of chemotherapy; and (4) the role of primary (or preoperative or neoadjuvant) chemotherapy. The next segment of this review will cover these four aspects.

Taxanes in adjuvant therapy. Paclitaxel was the first taxane available for clinical trials. As the results of the first two phase II trials in metastatic breast cancer became available, several groups initiated large randomized trials in the adjuvant setting to determine whether the addition of paclitaxel to an anthracycline-containing regimen provided an incremental benefit in relapse-free and OS. Over the past few years, the results of three such trials have been published or presented in abstract form.

The first to be reported, and the largest, was conducted by the CALGB (CALGB 9344).[59] The initial design was intended to assess the impact of escalating doses of doxorubicin as adjuvant therapy. A second randomization was incorporated into this trial to evaluate the impact of paclitaxel in early breast cancer. All patients received four cycles of a doxorubicin-cyclophosphamide (AC) combination, given at one of three doxorubicin doses. Subsequently, they were assigned to either four additional cycles of paclitaxel (175 mg/m^2 over 3 hours) or no additional chemotherapy, in a 3 $\times$ 2 factorial design. CALGB members recruited 3,121 women with lymph node–positive breast cancer to this study (Fig 1). The majority of patients with ER-positive tumors (94%) received tamoxifen following completion of chemotherapy. While the dose of doxorubicin failed to influence outcome at any time point, the first interim analysis in 1998 demonstrated a significant advantage from the addition of paclitaxel in terms of both relapse-free and OS. In the final analysis, performed in 2002 at a median follow-up of 69 months, the paclitaxel group maintained significantly greater 5-year disease-free survival (DFS; 70% *v* 65%; $P = .0023$) and OS (80% *v* 77%; $P = .0064$). In the National Surgical Adjuvant Breast and Bowel Project (NSABP) B28 trial,[60] 3,060 patients with node-positive, operable disease received four cycles of postoperative AC (A: 60 mg/m^2, C: 600 mg/m^2) at 21-day intervals, and then either four cycles of paclitaxel (225 mg/m^2 over 3 hours) every 3 weeks or no further chemotherapy. Patients younger than 50 years and ER-positive, and all those older than 50 years received tamoxifen 20 mg/d for 5 years; at a median follow-up of 65 months, the relative risk (RR) for disease recurrence favored the paclitaxel arm (RR = 0.83; $P = .008$), with no significant survival difference (RR = 0.94; $P = .46$).

Investigators at The University of Texas M. D. Anderson Cancer Center (Houston, TX) recently reported the results of a prospective randomized trial testing the contribution of paclitaxel to the combined modality management of primary breast cancer (ID94-002).[61] In this trial, 524 patients with operable primary breast cancer were randomly assigned to receive four cycles of paclitaxel followed by four cycles of FU, doxorubicin, and cyclophosphamide (FAC) or eight cycles of FAC (Fig 1). At a median follow-up of 4 years there was a 3% absolute difference in DFS favoring the paclitaxel arm, representing a 22% reduction in odds of recurrence. However, this difference did not reach statistical significance and no survival difference was seen.

Docetaxel became established as an effective agent for metastatic breast cancer soon after paclitaxel.[64] It was a natural progression from the results of the metastatic studies to initiate its evaluation in the adjuvant setting. Investigators from the Breast Cancer International Research Group (BCIRG) recently reported the results from the second interim analysis of the BCIRG 001 adjuvant trial,[62,63] which randomly assigned 1,491 patients with node-positive breast cancer to treatment with six cycles of docetaxel, doxorubicin, and cyclophosphamide (TAC) or FU, FAC given as adjuvant chemotherapy (Fig 1). At a median follow-up of 55 months, both DFS, the primary end point, and OS were significantly greater in the TAC group (75% *v* 68%; $P = .001$ and 87% *v* 81%; $P = .008$, respectively). Subgroup analyses according to ER status (positive *v* negative) and the degree of nodal involvement (one to three nodes positive *v* $\geq$ four nodes positive) failed to identify a subgroup that did not benefit from the docetaxel regimen. This benefit achieved statistical significance in the ER-positive, ER-negative, and one to three nodes subgroups. The therapeutic benefit came at the expense of increased toxicity: grade IV neutropenia was significantly more frequent in the TAC arm, and febrile neutropenia

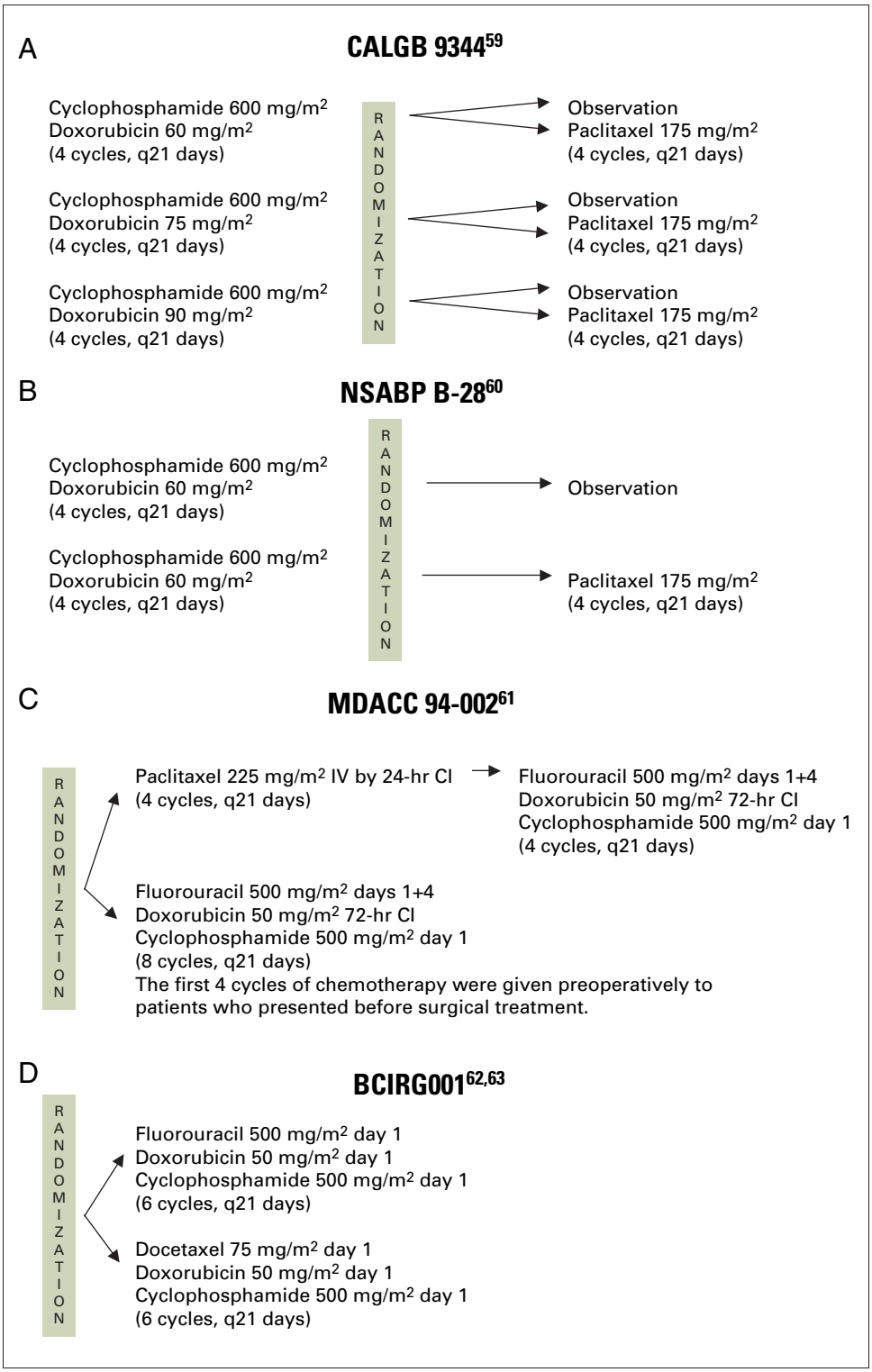

Fig 1. Design of taxane-containing adjuvant chemotherapy trials. (A) Cancer and Leukemia Group B (CALGB) 9344; (B) National Surgical Adjuvant Breast and Bowel Project (NSABP) B-28; (C) M. D. Anderson Cancer Center (MDACC) 94-002; and (D) Breast Cancer International Research Group (BCIRG) trial 001. IV, intravenous; CI, continous infusion.

increased 10-fold in the TAC arm compared to the control arm. However, there were no significant increases in toxic deaths between the two arms of the study.

In aggregate, these four trials, with more than 8,000 patients registered, demonstrated a modest, but significant, improvement in both DFS and OS from the addition of a taxane to an anthracycline-containing regimen The absolute magnitude of benefit from taxanes is uncertain, however, because the control regimen used in CALGB 9344 and NSABP B-28 was arguably suboptimal. Patients

in the control arms of these studies received only four cycles of treatment, while those in the experimental arms received eight. Four cycles of AC have been shown to be equivalent to, but not more effective than, six cycles of CMF, the gold standard that preceded the anthracycline combinations.[65] Three- or four-drug anthracycline-containing combinations, usually administered for six or more cycles, have been shown to be clearly superior to six cycles of CMF.[52,53,66-68] Therefore, it has been argued that the experimental arms of CALGB 9344 and NSABP B-28 have demonstrated that AC plus paclitaxel is superior to six cycles of CMF, but did not provide evidence of superiority to the "best" anthracycline regimens, such as the Canadian CEF (cyclophosphamide, epirubicin, and fluorouracil),[66] the French FEC_{100} (fluorouracil 500 mg/m^2, epirubicin 100 mg/m^2, and cyclophosphamide 500 mg/m^2),[69] or the M. D. Anderson Cancer Center's FAC.[70] Although the M. D. Anderson trial and the BCIRG trial compared equal durations of therapy, the benefit seen in NSABP B-28 and CALGB 9344 may be due to the effect of additional cycles of therapy as much as to the addition of paclitaxel. For this reason, several ongoing randomized trials are now comparing six cycles of CEF/FEC or FAC to four cycles of AC followed by four cycles of a taxane.

A multicenter trial compared the results of four cycles of AC (A: 60 mg/m^2, C: 600 mg/m^2) to those of four cycles of docetaxel (75 mg/m^2) and cyclophosphamide (600 mg/m^2).[71] Forty-eight percent of registered patients had axillary lymph node–negative breast cancer. With less than 2 years of median follow-up, no difference was observed between the two arms in either DFS or OS. Interpreted positively, this trial suggests that a non–anthracycline-containing regimen appears comparable to an anthracycline-containing regimen. The docetaxel and cyclophosphamide regimen is thus a valuable alternative to AC, most evidently in patients with concerns about cardiac toxicity. As is true for AC, however, this regimen is likely less active than the three-agent regimens in node-positive disease.

Toxicities in all four trials were manageable. While the addition of taxanes increased the incidence of myelosuppression, neurotoxicity, and fatigue, the rates of infection and septic death did not differ between the treatment arms.

The early results of several other prospective randomized trials assessing the role of taxanes in adjuvant therapy of primary breast cancer have been presented at several international conferences and are summarized in Table 1. Many worldwide adjuvant taxane studies are ongoing, and we eagerly await their results to better delineate the clinical role of paclitaxel and docetaxel in early breast cancer. It is estimated that more than 30,000 patients with primary breast cancer were recruited to first-generation, taxane-containing, adjuvant trials worldwide; another 25,000 are being recruited for second-generation trials containing taxanes.

Sequential single agents versus simultaneous combinations in the adjuvant setting. Over the past decade, there has been ongoing controversy about the best way to combine chemotherapeutic agents in early breast cancer. There is no argument about the need for multiple agents in order to achieve the highest level of control. There are, however, competing schools of thought regarding the sequential use of one agent at a time as opposed to the simultaneous administration of the same agents.[73] The controversy is based on theoretical considerations indicating that full doses of a drug given with the highest possible frequency will produce the highest degree of cell kill, and therefore offer the highest probability of cure.[74] The translation of this hypothesis to clinical trials assumed, as was customary in the 1980s and 1990s, that every cytotoxic agent had a steep linear dose-response correlation, and that the optimal effect could only be obtained by administering the

Table 1. Phase III Randomized Adjuvant Taxane Breast Cancer Trials

Study	No. of Patients	Median Follow-Up (months)	Comparison	5-Year DFS (%)	5-Year OS (%)
CALGB 9344[59]	3,121	69	AC × 4	65	77
			AC × 4 → P × 4	70*	80*
NSABP B-28[60]	3,060	65	AC × 4	72	85
			AC × 4→ P × 4	76*	85
Buzdar[61]	524	60	P → FAC	86	NR
			FAC → FAC	83	NR
BCIRG 001[62,63]	1,491	55	TAC × 6	75*	87*
			FAC × 6	68	81
CALGB 9741[72]	2,005	36	Dose-dense arms II and IV	82†	92
			Standard arms I and III	75*	90*
US Oncology[71]	1,016	22	AC × 4	99	97
			TC × 4	99	98

Abbreviations: DFS, disease-free survival; OS, overall survival; CALGB, Cancer and Leukemia Group B; AC, doxorubicin and cyclophosphamide; P, paclitaxel; NSABP, National Surgical Adjuvant Breast and Bowel Project; FAC, fluorouracil, doxorubicin, and cyclophosphamide; NR, not reported; BCIRG, Breast Cancer International Research Group; TAC, docetaxel, doxorubicin, and cyclophosphamide; TC, docetaxel and cyclophosphamide.

*$P < .05$.

†82% (4-year DFS).

maximally tolerated dose. Since all anticancer drugs have substantial and varied side effects, simultaneous combinations usually require reductions in dose for most or all components to avoid severe or life-threatening toxicity. Under these assumptions it was appropriate to test the hypothesis and compare the sequential administration of single agents to simultaneous administration of a combination regimen of the same drugs.

The Southwest Oncology Group (SWOG) was the first to test this hypothesis in protocol SWOG 9313.[75] In this study, four cycles of doxorubicin (81 mg/m^2) were administered at a 21-day interval, followed by three cycles of cyclophosphamide (2,400 mg/m^2) given at a 2-week interval. This treatment was compared in 3,176 patients with six cycles of doxorubicin (54 mg/m^2) in combination with cyclophosphamide (1,200 mg/m^2). While the first arm had significantly higher dose-intensity, the total doses of both drugs and the duration of therapy were the same in both arms. After 5.3 years of follow-up there was no difference in outcome between the two arms, but the sequential arm had significantly greater hematologic and gastrointestinal toxicity.

Other studies have since demonstrated that the dose-response correlation is seldom, if ever, linear, and that for both doxorubicin and cyclophosphamide, dose-increments above a certain dose, which is far below the maximum-tolerated dose, produce increased toxicity without survival benefit.[59,76,77] Therefore, the current standard doses (60 and 600 mg/m^2, respectively) in the commonly employed doxorubicin and cyclophosphamide combination appear optimal, whether given simultaneously or sequentially. Additional randomized trials have failed to demonstrate a significant dose response effect for the taxanes.

The role of dose-dense regimens in the adjuvant setting. A second important trial assessing the role of sequential and simultaneous combinations was CALGB 9741.[72] This study recruited 2,005 women with operable disease and lymph node involvement into a 2 × 2 factorial design. The first randomization was between concurrent doxorubicin (A; 60 mg/m^2) and cyclophosphamide (C; 600 mg/m^2) for four cycles, followed by paclitaxel (T; 175 mg/m^2 over 3 hours) for four cycles (AC → T), and sequential paclitaxel, doxorubicin, and cyclophosphamide, each for four cycles and using the same doses (A → T → C). The second randomization was between the standard 3-weekly dose interval, and a dose-dense 2-weekly interval, supported by G-CSF (filgrastim) on days 3 to 10 of each cycle. Patients were thus randomly assigned to one of four groups: (1) A → T → C every 3 weeks; (2) A → T → C every 2 weeks with G-CSF; (3) AC → T every 3 weeks; and (4) AC → T every 2 weeks with G-CSF. The primary end point was DFS. The design of this study permitted a clean comparison of standard and dose-dense schedules. The design was imperfect, however, as regards the impact of sequential versus simultaneous drug administration, since both arms contained sequential elements. At a median follow-up of 36 months, patients treated with the dose-dense (every 2 weeks) regimens (groups 2 and 4) had significantly higher DFS than those receiving conventional every-3-week dosing (groups 1 and 3). The projected 4-year DFS rate was 82% for the dose-dense arms compared to 75% for the every-3-week arms ($P = .013$). There was also a significant benefit in OS favoring the dose-dense arms. No significant difference in DFS was noted between the concurrent and the sequential schedules. Grade 4 neutropenia was more frequent in patients treated with the 3-weekly schedule than in those receiving the 2-weekly schedule (33% *v* 6%; $P < .0001$), since those in the latter group were protected by filgrastim administration. Overall, neutropenic fever and cardiac toxicity were rare. The combination arm administered every 2 weeks was associated with an increased rate of anemia.

Optimal timing of systemic chemotherapy: Adjuvant or neoadjuvant? Systemic therapy has traditionally been administered postoperatively, but is increasingly utilized in the preoperative or neoadjuvant setting.[78] For several decades, preoperative chemotherapy has been the preferred strategy to incorporate chemotherapy into multimodality therapy for patients with locally advanced breast cancer or inflammatory breast cancer.[79] The combination of neoadjuvant chemotherapy, surgical resection, and radiotherapy has significantly improved the survival rates of these patients, and numerous studies have now evaluated its use in operable breast cancer.[80]

The largest of the randomized studies comparing preoperative (neoadjuvant) to postoperative (adjuvant) chemotherapy was the NSABP B-18 study.[81-83] This study randomized 1,523 women with operable breast cancer to receive four cycles of AC either preoperatively or postoperatively. Although the survival rates were identical in the two arms of the study, preoperative chemotherapy improved the breast conservation rate. In addition, it was noted that pathologic complete response (pCR) in patients who received neoadjuvant therapy was a powerful prognostic marker for both DFS and OS. This association between pCR and survival has since been confirmed in several other studies.[84-86] Hence, although definitions of pCR vary across studies (breast only[81,87] *v* breast and axilla,[84-86] no tumor *v* no invasive tumor), and the rigor of the pathologic evaluation of breast tissue also varies widely, pCR rate is considered an extremely valuable end point in trials of preoperative chemotherapy regimens.

Neoadjuvant therapy thus has a few advantages over adjuvant therapy: (1) it provides higher rates of breast conservation,[80,81,88-90] (2) response to therapy can be assessed in real time, so that ineffective therapies can be abandoned in favor of alternative, non–cross-resistant

regimens, and (3) prognosis can be refined according to the degree of residual disease after therapy.

The majority of published studies of preoperative chemotherapy are small and nonrandomized. Most have used anthracycline-based regimens (with or without taxanes) for four to six cycles. Neoadjuvant regimens that do not contain trastuzumab generally produce pCR rates in the range of 10% to 30%. As preoperative administration of chemotherapy in itself does not improve survival, there are therefore only a handful of recent studies that contribute significantly to our knowledge regarding management of early breast cancer (Table 2).

Therasse et al[95] reported the results of a randomized trial comparing six cycles of cyclophosphamide (C; 75 mg/m^2 orally days 1 to 14), epirubicin (E; 60 mg/m^2 IV days 1, 8), and FU (500 mg/m^2 IV days 1, 8) administered every 28 days versus six cycles of E (120 mg/m^2 IV day 1), C (830 mg/m^2 IV day 1), and G-CSF (filgrastim; 5 μg/kg/d subcutaneously days 2 to 13) given every 14 days. Four hundred forty-eight patients with locally advanced breast cancer were enrolled over a period of 3 years. The median dose intensities delivered for C and E were 85% and 87%, respectively, of that planned in the CEF arm, and 96% and 95% of that planned in the EC arm. After a median follow-up of 5.5 years, the median PFS was 34 and 33.7 months for CEF and EC, respectively ($P = .68$), and the 5-year survival rate was 53% and 51% for CEF and EC, respectively ($P = .94$). The dose-dense arm was associated with more nausea, vomiting, and anemia, but fewer episodes of febrile neutropenia.

Protocol B-27 was the NSABP's second randomized trial assessing preoperative chemotherapy.[87] In this study, 2,411 patients with operable primary breast cancer were randomly assigned to four cycles of preoperative AC, four cycles of preoperative AC followed by four cycles of preoperative docetaxel (100 mg/m^2 IV every 3 weeks), or four cycles of AC followed by surgery and four cycles of postoperative docetaxel. Compared to preoperative AC alone, preoperative AC followed by preoperative docetaxel increased the clinical complete response rate (40.1% *v* 63.6%; $P < .001$), the overall clinical response rate (85.5% *v* 90.7%; $P < .001$), the pathologic complete response rate (13.7% *v* 26.1%; $P < .001$), and the proportion of patients with negative nodes (50.8% *v* 58.2%; $P < .001$). This study complements CALGB 9344 and NSABP B28, confirming the incremental benefit of adding a taxane to AC.

Smith and collaborators[91] reported the results of a multicenter study (the Aberdeen trial[96]) in 162 patients with large operable and locally advanced breast cancer. All received four cycles of doxorubicin, cyclophosphamide, vincristine, and prednisolone (CVAP); those who responded were randomly assigned to receive four more cycles of CVAP or four cycles of docetaxel (100 mg/m^2). All nonresponders received four cycles of docetaxel. The clinical complete remission (CR) and clinical partial remission rate (94% *v* 66%; $P = .001$) and pathologic CR (34% *v* 16%; $P = .04$) rates were higher for those who were randomly assigned to receive docetaxel. This improvement in response rates translated into longer relapse-free and OS rates.[96] In this small study, treatment was of equal duration in both arms, so the improved outcome could only be attributed to the introduction of docetaxel. The study results confirm that improvements in pathological CR rates are associated with improvement in relapse-free and OS.

At the 2002 ASCO Annual Meeting, von Minckwitz et al[92] reported the results of the GEPAR-DUO randomized study. Nine hundred thirteen patients with large operable breast cancer were randomly assigned to be treated preoperatively with four cycles of dose-dense doxorubicin and docetaxel every 2 weeks, or four cycles of standard AC followed by four cycles of docetaxel. At the second interim analysis, the trial was closed to patient accrual because of a significantly higher pCR rate for the AC-docetaxel regimen (24.7% *v* 5.2%). Toxicity was higher in the AC-docetaxel arm. These and several other trials investigating dose-dense regimens have less than optimal designs to assess

Table 2. Phase III Randomized Neoadjuvant Taxane Breast Cancer Trials

Study	No. of Patients	Treatment Regimens	ORR	pCR	Breast Conservation Rate	5-Year DFS (%)	5-Year OS (%)
Aberdeen[91]	162	CVAP × 8	94	34	67	93	97
		CVAP→ docetaxel	66	16	48	74	72
NSABP B27[7]	2,411	AC × 4	85	14	61	NR	NR
		AC × 4→ docetaxelx4	91	26	63	NR	NR
GEPAR-DUO[92]	913	ADOC × 4	NR	22	NR	NR	NR
		AC × 4→ docetaxel × 4	NR	12	NR	NR	NR
AGO[93]	631	E × 3→ docetaxel × 3	NR	18	66	NR	NR
		ET × 4	NR	10	55	NR	NR
Green[94]	258	Weekly P × 12→ FAC × 4		29		NR	NR
		Every-3-week P × → FAC × 4		14		NR	NR

Abbreviations: ORR, overall response rate; pCR, pathologic complete response; DFS: disease-free survival; OS, overall survival; CVAP: cyclophosphamide, vincristine, doxorubicin, prednisolone; NSABP, National Surgical Adjuvant Breast and Bowel Project; AC, doxorubicin and cyclophosphamide; NR: not reported; ADOC, doxorubicin and docetaxel; AGO, Arbeitgemeinschaft fur Gynakologische Onkologie; E: epirubicin; ET, epirubicin and docetaxel; P: paclitaxel; FAC, fluorouracil, doxorubicin, and cyclophosphamide.

the contribution of dose density to adjuvant therapy, since they include multiple modifications in dose, schedule, and the number of agents, in addition to dose-dense schedules of administration. These additional variables complicate the interpretation of these trials.

Untch et al[93] reported the results of the AGO study at the 2002 ASCO Annual Meeting. Six-hundred thirty-one patients with operable breast cancer were randomly assigned to three cycles of dose-dense epirubicin followed by three cycles of dose-dense paclitaxel or four cycles of combined epirubicin and paclitaxel. The pCR rates were 18% and 10%, respectively, and the rate of breast conservation was higher with the dose-dense regimen.

Green et al[94] reported the results of a randomized trial of preoperative chemotherapy comparing 12 weekly doses of paclitaxel (80 mg/m^2) followed by four cycles of FAC with four 3-weekly doses of paclitaxel (225 mg/m^2) also followed by four cycles of FAC in 258 patients with operable breast cancer. pCR rates were 29% and 13% for those treated with weekly and 3-weekly paclitaxel, respectively ($P = .01$). Similar results were subsequently reported in a metastatic setting,[6] and are further tested in ECOG trial E1199.

A large number of relatively small phase II trials of neoadjuvant therapy in operable breast cancer was reported over the past 5 years.[97-142] Combinations of doxorubicin and paclitaxel, epirubicin and paclitaxel, doxorubicin and docetaxel, epirubicin and docetaxel, a taxane and a platinum salt, or other two- or three-drug combinations were tested. Overall response rates were high, while pCR rates ranged 3% to 42%. There was a trend toward higher pCR rated with taxane and anthracycline combinations, and this would be consistent with the randomized trials described above. Additional randomized trials are ongoing to determine the optimal dose, sequence, and composition of preoperative chemotherapy regimens. These regimens utilize at least four cycles, and often eight cycles, of chemotherapy before definitive surgical resection of the primary. Outside of a clinical trial, four cycles of an anthracycline-containing regimen sequenced with four cycles of a taxane given before surgery appear to produce optimal reduction in tumor volume.

CONTROVERSIES AND FUTURE DIRECTIONS

An increasingly difficult problem with all these regimens is the high cost of treatment. The cost of commonly used adjuvant chemotherapy regimens is described in Table 3. The quoted costs are limited to the average wholesale price of cytotoxics and filgrastim alone, and assume a 1.6m^2 body-surface area. Specifically, the cost of antiemetics and administration has not been addressed. These figures indicate that there are significant differences in the cost of various commonly used regimens. Although the cost of these drug combinations will vary from country to country, the use of epirubicin, taxanes, and/or the prophylactic use of filgrastim markedly increases the cost of adjuvant chemotherapy regimens. Cost is thus one of several considerations in the selection of optimal therapy for an individual patient.

Table 3. Cost of Adjuvant Chemotherapy Regimens (based on a body-surface area of 1.6 m^2)

Regimen	Drug Cost for Entire Treatment (US$)
Adjuvant	
Classical (oral) CMF (6 cycles)	1,152
IV CMF (6 cycles)	391
NSABP AC (4 cycles)	828
MDACC FAC (6 cycles)	1,087
CALGB CAF (6 cycles)	1,304
CEF (6 cycles)	17,006
FEC_{100} (6 cycles)	13,877
AC (4 cycles) → P (4 cycles)	7,374
P (4 cycles) → FAC (4 cycles)	7,271
Weekly P × 12 → FAC (4 cycles)	9,703
Docetaxel + AC (6 cycles)	12,885
Dose-dense	
AC (4 cycles) → P (4 cycles) every 2 weeks + G-CSF (65 kg patient)	20,121
AC (4 cycles) → P (4 cycles) every 2 weeks + G-CSF (85 kg patient)	27,681
A × 4 → P ×4 → C × 4 + G-CSF (65 kg)	26,495
A × 4 → P × 4 → C × 4 + G-CSF (85 kg)	37,835

Abbreviations: CMF, cyclophosphamide, methotrexate; and fluorouracil; IV, intravenous; NSABP, National Surgical Adjuvant Breast and Bowel Project; AC, doxorubicin and cyclophosphamide; MDACC, M.D. Anderson Cancer Center; FAC, fluorouracil, doxorubicin, and cyclophosphamide; CALGB, Cancer and Leukemia Group B; CAF, cyclophosphamide, doxorubicin, and fluorouracil; CEF, cyclophosphamide, epirubicin, and fluorouracil; FEC_{100}, fluorouracil 500 mg/m^2, epirubicin 100 mg/m^2, and cyclophosphamide 500 mg/m^2; P, paclitaxel; G-CSF, granulocyte colony-stimulating factor (filgrastim); C, cyclophosphamide.

For patients with residual disease in the breast and/or axilla after current maximum therapy, should additional therapy be given? Currently, there are no data to support the administration of additional therapy in this setting. Two recently reported studies evaluated this issue of patients with a poor clinical response to an initial neoadjuvant chemotherapy regimen. In the Aberdeen study,[96] the patients who had no clinical response to CVAP and then were crossed over to docetaxel achieved only a 2% pCR. An additional study similarly examined the cross-over effect on pCR rates. In that study, 41 patients were treated preoperatively with TAC (docetaxel, doxorubicin, and cyclophosphamide). Those with no clinical response were randomly assigned to continue TAC or receive the potentially non–cross-resistant combination of vinorelbine and capecitabine. As seen in the Aberdeen trial, [96] the nonresponders to the initial chemotherapy regimen had a very low probability of achieving a pCR with further therapy (4% to 7%), but the fact that any pCRs were seen after failure of a three-drug regimen is of interest. These studies, though small, may reflect the biology of a given tumor in

assessing whether a tumor will respond to any cytotoxic agents. New agents are clearly needed to address this challenging situation.

Pathologic CR provides a strong correlation with long-term outcome. However, this correlation might not have the same utility for all patients with breast cancer. Several series have demonstrated that pCR rates with the same chemotherapy regimens are several-fold higher for patients with ER-negative breast cancer, compared to ER-positive tumors.[142-144] Similarly, there are reports that suggest that pCR rate is significantly higher for patients with ductal carcinoma than for patients with lobular breast cancer.[145,146] The pCR rates for patients with ER-positive and/or lobular carcinoma range from 3% to 5%, similar to the pCR rates reported after neoadjuvant endocrine therapy with tamoxifen or aromatase inhibitors in patients with ER-positive tumors. No correlation of pCR and long-term survival has been demonstrated in these groups. Furthermore, pCR is documented after several cycles of chemotherapy (three to six cycles) or several months of endocrine therapy. Are there means to accurately predict whether pCR will occur after a specific treatment? Many predictive markers regarding response and survival have been explored retrospectively and prospectively, including ER, progesterone receptor, *HER-2/neu*, and *p53*.[147] These studies have produced conflicting results, demonstrating the difficulty in identifying reliable markers of response. No single marker can predict response to therapy with any degree of certainty for individual patients. High throughput techniques, such as microarray gene profiling and proteomics, are being investigated to develop multimarker models that can be used to accurately predict pCR.[148,149]

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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