Original Article

Taxanes in the Adjuvant Treatment of Breast Cancer

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Key Words

Breast neoplasms, adjuvant therapy, taxanes, paclitaxel, docetaxel

Abstract

Adjuvant chemotherapy clearly demonstrates a reduction in mortality in breast cancer. However, the added benefit from the addition of taxanes remains uncertain. Paclitaxel and its cousin docetaxel have proven activity in the treatment of metastatic breast cancer. Toxicity has been tolerable when taxanes are used as single agents or in combination with anthracyclines. Several clinical trials are currently underway evaluating the role of taxanes in the adjuvant setting. Preliminary results from large phase III studies are promising; however, mature data are required before conclusions can be drawn. This article reviews the trials currently underway, evaluating the efficacy, dosage, scheduling, and regimens of taxanes in the adjuvant treatment of breast cancer. (*JNCCN* 2003;1:222–231)

Over the past decade, several major advances in the adjuvant treatment of breast cancer have enhanced a woman's likelihood of long-term survival. Physicians have long understood that clinically undetectable micrometastatic disease exists in most breast cancer patients at the time of initial diagnosis. Even after effective local therapy, many patients manifest metastatic involvement with the passage of time, and improvements in local control have demonstrated at best a small reduction in the incidence of distant metastases.[1] Theoretically, adjuvant systemic therapy effectively inhibits or destroys these micrometastases after primary surgery, thus improving disease-free survival.

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Since the late 1980s, the Early Breast Cancer Trialists' Collaborative Group overviews meaningfully showed the effectiveness of adjuvant systemic therapy on long-term survival, generating widespread acceptance for the clinical value of adjuvant systemic therapy.[2–4] These meta-analyses also show that combination chemotherapy or polychemotherapy is more effective than single-agent treatment.[2–4] Furthermore, the analyses reveal that anthracycline-based therapy provides slightly greater benefit than regimens without anthracyclines, with approximately a 10% improvement in the risk for disease recurrence or mortality.[4,5]

Over the past decade, taxanes have been investigated in breast cancer treatment. These anticancer drugs, which have demonstrated substantial activity as single agents against metastatic breast cancer as well as in combination,[6–8] are exciting additions to our arsenal of adjuvant anticancer agents. Both paclitaxel and docetaxel have shown activity in anthracycline-resistant breast cancer,[9] and undoubtedly represent the most active chemotherapeutic agents developed over the past decade for the treatment of advanced breast cancer. With multiple randomized clinical trials currently underway, investigators are rigorously examining the role of these agents in the adjuvant and neoadjuvant settings. This review focuses on the results of recently completed taxane studies and outlines issues still to be resolved. Specifically, mechanisms of action, toxicities, and clinical activity of taxanes are addressed. In addition, the ongoing evaluation of taxanes in investigational trials will be discussed.

Mechanisms of Action

The taxanes currently available for clinical use are paclitaxel and docetaxel. These agents have similar, although not identical, mechanisms of action, namely disruption of the microtubule network by binding to

dimeric tubulin. Consequently, stable microtubule bundles accumulate in the cell while taxanes work to inhibit tubule disassembly.[10,11] Cells exposed to taxanes are incapable of forming normal mitotic spindles and become blocked in the G2 and M phases of the cell cycle. The dysfunctional microtubules disrupt normal microtubule dynamics, leading to cell death. Both taxanes have potent radiosensitizing effects, can induce apoptosis, and have anti-angiogenic properties.[12–15]

Although they share a common binding site and similar mechanism of action, paclitaxel and docetaxel each possess unique chemical and pharmacologic characteristics, which probably account for differences in their potencies in vitro. Docetaxel has linear pharmacokinetics, a longer plasma half-life, and longer intracellular retention. It has shown a 1.9-fold greater affinity for binding the (β-tubulin subunit than paclitaxel.[16–19]

Paclitaxel Clinical Activity

Paclitaxel (Taxol) was the first taxane approved in the United States for use in metastatic breast cancer. Identified in 1963 as the active component of a bark extract from the Pacific yew *Taxus brevifolia*,[20] paclitaxel was initially approved for the treatment of epithelial ovarian cancer in 1992.[21] Subsequent extensive phase II trials ensued, revealing significant activity in head and neck, lung, bladder, and breast cancer.[22]

In 1991, Holmes et al evaluated the use of taxanes in breast cancer.[23] In that study, 25 chemotherapy-naïve patients were treated with 250 mg/m^2 infused over 24 hours. Three complete and 11 partial responses occurred, for an overall response rate of 56%. Subsequent efforts by several investigators, including Reichman et al[24] and Seidman et al,[25] confirmed both the activity and dosing schedule established in Holmes et al's initial work,[23] with response rates ranging from 32% to 62%. Used as a second-line agent, paclitaxel still shows impressive response rates (10% to 44% depending on dose and schedule).[26–29]

Dose and Schedule

The optimal dose and schedule for paclitaxel have undergone extensive investigation but as yet are unresolved. Initial studies used high doses to 250 mg/m^2, which caused severe myelotoxicity and required growth factor support. In a sizable phase III study evaluating dose escalation, Nabholtz et al[30] found no significant difference in overall response rates between doses of 135 mg/m^2 and 175 mg/m^2, although time to progression (TTP) was slightly improved in the cohort receiving 175 mg/m^2. A smaller study by Gianni et al[31] confirmed that the dose escalation to 225 mg/m^2 did not improve outcome. The CALGB conducted a study in which 325 patients were randomized to receive 175, 210, or 250 mg/m^2 administered over three hours. Consistent with Nabholtz et al's findings, TTP was prolonged by higher doses, and response rates and overall survival were similar.[32] The results of these trials led to regulatory approval of paclitaxel at a dose of 175 mg/m^2 over a period of three hours in patients with advanced breast cancer. This dose has been extrapolated for use in the adjuvant setting as well.

Several investigators evaluated weekly paclitaxel at doses of 80 to 100 mg/m^2, taking advantage of the equivalent efficacy and decreased toxicity seen with shorter paclitaxel infusions. Two separate phase II studies yielded response rates of 53% and 22%, respectively, in patients heavily pretreated with anthracyclines.[33,34] A prospective randomized trial (CALGB) comparing weekly paclitaxel to an every three week schedule in metastatic breast cancer is presently underway.

Docetaxel Clinical Activity

Docetaxel, which is both structurally and mechanistically similar to paclitaxel, is the second taxane evaluated in clinical trials. Docetaxel is a semisynthetic product derived from the European yew *Taxus baccata*.[35] Like paclitaxel, docetaxel was found to have activity against a variety of tumor types including breast, colon, ovarian, sarcoma, and bladder. Although structurally and mechanistically similar to paclitaxel, docetaxel has several distinguishing features. For instance, although docetaxel and paclitaxel share the same microtubule-binding site, docetaxel seems to bind with higher affinity. In addition, docetaxel may accumulate to higher intracellular concentrations and have slower efflux than paclitaxel.[36]

Docetaxel has shown remarkable clinical activity as first-line therapy for metastatic breast cancer. Early clinical data from phase II trials show response rates in chemotherapy-naïve patients ranging from 54% to 68% at a docetaxel dose of 100 mg/m^2.[37–39] In heavily pretreated patients, docetaxel is also effective, with response rates between 35% and 60%.[40–43]

Interestingly, resistance to docetaxel appears to be less influenced by MDR proteins; therefore, paclitaxel and docetaxel may not be entirely cross-resistant. In a study by Valero et al,[43] 25% of 44 patients who progressed during treatment with paclitaxel responded to salvage therapy with docetaxel.

Dose and Schedule

Dose and scheduling were established early in the phase I experience, with docetaxel at 100 mg/m^2. Response rates of 50% to 67.5% were seen in with docetaxel administered as a one-hour infusion every three weeks. Lower dosages were evaluated in hopes of decreasing toxicity due to fluid retention. However, efficacy appeared to decrease without changing the incidence or severity of fluid retention.[39] Evaluation of weekly docetaxel doses of 30 to 40 mg/m^2 per week over one hour in women with metastatic breast cancer produced responses in 41% of patients in one study, without evidence of increased toxicity.[44]

Combination Regimens

Success with single agent taxanes and the observed lack of complete cross-resistance logically led to the incorporation of taxanes into combination regimens. Both paclitaxel and docetaxel have been combined with other cytotoxic agents in the metastatic setting in hopes of improving response rates and prolonging survival. Response rates between 46% and 94% have been reported in several phase II trials of paclitaxel and doxorubicin; however, heart failure was observed in up to 20% of patients.[45–48]

Pharmacologic studies of combination therapy found a 31% decrease in doxorubicin clearance when paclitaxel is administered first, resulting in higher drug levels.[49] Three year follow-up of Gianni et al's original cohort found the cardiac toxicity reversible, with no change in left ventricular ejection fraction. However, investigators have recommended limiting the cumulative doxorubicin dose to less than 360 mg/m^2.[50] Paclitaxel has been combined with mitoxantrone and epirubicin in phase II trials without increased cardiotoxicity.[51]

Promising early experience with docetaxel prompted evaluation of combinations with other agents in the first-line treatment of metastatic breast cancer. Combinations of docetaxel and anthracyclines have yielded overall response rates of 53% to 80% in several small phase I and II studies,[52,53] without causing excess cardiotoxicity.[54] This favorable efficacy and safety data led to two larger phase III trials: Tax 306 and Tax 307. These trials showed significantly improved response rates in the arms involving taxanes, although overall survival (OS) was not significantly improved. These favorable results prompted further evaluation of taxanes in the adjuvant setting.

Toxicity

Profound myelosuppression, which is usually transient and noncumulative, is the major dose-limiting toxicity of both taxanes. Neutropenia is more severe with longer paclitaxel infusion regimens and in patients who have received extensive previous myelotoxic therapy.[55]

Another challenging problem encountered with the administration of both taxanes is a hypersensitivity reaction (HSR). Development of paclitaxel was initially delayed due to the high incidence of severe HSR observed in some studies, up to 25% to 30% of patients.[39,56] Serious reactions usually occurred within two to three minutes of administration of the first or second dose of paclitaxel, and almost all occurred within 10 minutes. Patients recovered fully after the taxane was discontinued and antihistamines, steroids, fluids, and sometimes vasopressors were given. The consequent development of a premedication schedule of corticosteroids and antihistamines has been effectively used in most subsequent phase II and III studies. To reduce the risk of subsequent HSR, patients can be given 20 mg of dexamethasone orally or intravenously 12 and 6 hours before treatment, 50 mg of diphenhydramine intravenously 30 minutes before treatment, and a histamine H_2 antagonist such as cimetidine 300 mg intravenously 30 minutes before treatment. This results in only a 1% to 3% incidence of HSR.[40,41]

Although early evaluations of docetaxel did not yield a high HSR frequency, later phase II data showed an incidence of 25% to 30%. Premedication with a three-day regimen of oral dexamethasone, 8 mg twice a day beginning 24 hours before infusion, is now recommended. Successful retreatment after significant HSR has been documented with both paclitaxel and docetaxel.

Paclitaxel induces a peripheral neuropathy characterized by numbness and paresthesias in a stocking-

and-glove distribution. Sensory symptoms can occur as soon as 24 to 72 hours after treatment with higher doses and shorter infusions of paclitaxel, and may become more severe with cumulative dosing or with concomitant treatment with other neurotoxic agents.[57] Rarely, motor and autonomic dysfunctions are seen, especially at higher doses of taxanes and in patients with pre-existing neuropathies. Five to 15% of patients develop an arthralgia-myalgia syndrome two to five days after therapy with paclitaxel, with severity ranging from mild to debilitating pain. This syndrome is more prominent with shorter duration infusion schedules but may be preventable with oral glutamine or corticosteroid use.[58]

Disturbances in cardiac rhythm, typically a transient asymptomatic bradycardia, have been seen with paclitaxel but not docetaxel.[59,60] Rarely, more dangerous bradyarrhythmias, including Wenckebach's syndrome and Mobitz type II as well as third degree block, also have been reported with paclitaxel use. However, the reported incidence is only 0.1%,[44] and most documented episodes have been asymptomatic and reversible.

Like most cytotoxic agents, taxanes induce reversible alopecia of the scalp and loss of body hair. Drug-related gastrointestinal effects, such as vomiting or diarrhea, are less common, although high doses have been reported to cause mucositis. Cellulitis has been reported following extravasation of paclitaxel.[61] Urticaria, dermatitis, and reactive erythema occur in up to two thirds of patients.

Severe fluid retention occurs uniquely with docetaxel, manifesting as gradual progression of peripheral edema and pleural effusions. The manifestation of this syndrome can be reduced by premedication using dexamethasone and may be completely, albeit slowly, reversible with oral diuretics.[62]

Skin and nail toxicity are also unique to docetaxel. For patients with hepatic compromise, docetaxel at a dose of 100 mg/m^2 causes unacceptable toxicity. Therefore, these patients should be treated especially cautiously, with dose reductions and careful hematologic monitoring.

Review of the Trials

With the noteworthy antitumor effect of taxanes in first-line treatment of metastatic breast cancer, the logical progression was to explore activity in the adjuvant setting. Small phase I or II studies proved the safety and efficacy of including taxanes after standard doxorubicin/cyclophosphamide treatment.[63] Preliminary results are currently available from two large randomized trials, while several studies recently have completed accrual, and many other trials are ongoing to evaluate the optimal application of taxanes in the adjuvant treatment of breast cancer.

The first study to produce results with the adjuvant use of taxanes was CALGB 9344. This large Intergroup phase III randomized trial evaluated doxorubicin dose intensity and the efficacy of sequentially combining paclitaxel with the AC regimen in patients with node positive breast cancer. In the trial schema, patients were randomized to three different doses of doxorubicin for four cycles, and then four doses of paclitaxel (175 mg/m^2) over three hours versus observation (Table 1). After completion of chemotherapy, estrogen receptor- and progesterone receptor-positive patients received tamoxifen.

Preliminary results from the study were promising. An interim analysis at a median follow-up of 21 months revealed statistically significant reductions in recurrence (22%) as well as mortality (26%) in patients receiving paclitaxel ($P < .05$).[64] Results of a second interim analysis at 30 months of follow-up, presented to the FDA in April 1999, continued to show a reduction in recurrence and mortality. These results won paclitaxel approval for use in adjuvant therapy in breast cancer. After five years of follow–up, more mature results of this trial were presented at the November 2000 NIH Consensus Conference. At a median 52 months follow-up, statistically significant benefits persisted in recurrence risk, but only by 13% ($P < .05$).[65] Maturing data from this study continue to show a survival advantage of approximately 4% for the paclitaxel-treated patients.[66]

An unplanned retrospective subset analysis of the CALGB 9344 data surprisingly revealed that most of the benefit derived from paclitaxel occurred in patients with receptor-negative tumors. For disease-free and overall survival, advantages of 25% and 22% were noted, respectively, compared with little benefit seen in receptor-positive patients.[67] The explanation for this potential difference is unclear, and further follow-up is needed to determine the ultimate impact of paclitaxel on this subgroup of patients.

The National Surgical Adjuvant Breast Project (NSABP) also evaluated the benefit of adjuvant taxane therapy. NSABP B-28 is a large phase III trial accessing the role of taxanes in addition to conventional

Table 1 Completed and Accruing Trials, Data Outstanding

Trial	Eligibility	Design
Sequential Therapy		
CALGB 9344	Node +	AC (60, 75, 90/600 mg/m²) ↔ 4 +/– PAC (175 mg/m²)
NSABP B-28	Node +	AC (60/600 mg/m²) ↔ 4 +/- PAC (225 mg/m²)
MD Anderson Study	Node ±	PAC (175 mg/m²) ↔ 4 + FAC ↔ 4 Surgery FAC ↔ 8
BIG	Node +	AT (60/60 mg/m²) ↔ 4 × CMF ↔ 3 AC (60/600 mg/m²) ↔ 4 × CMF ↔ 3 A (60 mg/m²) ↔ 4 × CMF ↔ 3 A (60 mg/m²) ↔ 3 × T (100 mg/m²) ↔ 3 × CMF ↔ 3
Italian Adjuvant Study Group	Node +	E (120 mg/m²) ↔ 4 × CMF ↔ 4 E(120 mg/m²) ↔ 4 × T(100 mg/m²) ↔ 4 × CMF ↔ 4
French Cooperative Adjuvant Study	Node +	FEC ↔ 6 FEC ↔ 3 × T (100 mg/m²) ↔ 3
		ECOG 1199 Node ± Her2- AC (60/600 mg/m²) ↔ 4 × T (100 mg/m²) q3 wk ↔ 4 AC (60/600 mg/m²) ↔ 4 × PAC (175 mg/m²) q3 wk ↔ 4 AC (60/600 mg/m²) ↔ 4 × T (35 mg/m²) weekly ↔ 12 AC (60/600 mg/m²) ↔ 4 × PAC(80 mg/m²) weekly ↔ 12
CALGB 9741	Node +	A q3 wk ↔ 4 × PAC q3 wk x4 × C q3 wk ↔ 4 A q2 wk ↔ 4 × PAC q2 wk ↔ 4 × C q2 wk ↔ 4 AC q3 wk ↔ 4 × PAC q3 wk ↔ 4 AC q2 wk ↔ 4 × PAC q2 wk ↔ 2
Concurrent Therapy		
ECOG 2197	Node ±	AT (60/60 mg/m²) ↔ 4 AC (60/600 mg/m²) ↔ 4
NSABP B-30	Node +	AC(60/600 mg/m²) ↔ 4 × T (100 mg/m²) ↔ 4 AT(50/75 mg/m²) ↔ 4 TAC ↔ 4
BCIRG 005	Her2–	TAC ↔ 6 AC (60/600 mg/m²) ↔ 4 × PAC (175 mg/m²) ↔ 4
NCCTG – Intergroup 981	Node +	EC (100/500 mg/m²) ET (100/75 mg/m²)
NCIC-CTG	Node ±	FEC ↔ 6 AC (60/600 mg/m²) ↔ 4 × PAC (175 mg/m²) ↔ 4 EC (100/500 mg/m²) q2 wk ↔ 6 × PAC (175 mg/m²) ↔ 4 + G-CSF + Erythropoietin
Neoadjuvant Therapy		
NSABP B-27	Node +	AC(60/600 mg/m²) ↔ 4 × surgery × RT AC(60/600 mg/m²) ↔ 4 × T(100 mg/m²) ↔ 4 × surgery × RT AC(60/600 mg/m²) ↔ 4 × surgery × T(100 mg/m²) ↔ 4 × RT
Aberdeen Neoadjuvant Study	Node ±	No response × T(100 mg/m²) ↔ 4 4 ↔ CVAP Response × T(100 mg/m²) ↔ 4 [or] CVAP ↔ 4
Taxane + Trastuzumab		
BCIRG 006	Her2+	AC (60/600 mg/m²) ↔ 4 × T (100 mg/m²) ↔ 4 AC (60/600 mg/m²) ↔ 4 × T (100 mg/m²) ↔ 4 + Trastuzumab TCH ↔ 6
NSABP B-31	Her2+, Node +	↗ Herceptin ↔ 1 yr AC (60/600 mg/m²) ↔ 4 × PAC (175 mg/m²) ↔ 4 ↘ Observation

Abbreviations are: A, doxorubicin; C, cyclophosphamide; T, docetaxel; PAC, paclitaxel; E, epirubicin; CVAP, cyclophosphamide, vincristine, doxorubicin and prednisone; CMF, cyclophosphamide, methotrexate and fluorouracil; FAC, 5-fluorouracil 500 mg/m², doxorubicin 50 mg/m² and cyclophosphamide 500 mg/m²; FEC, 5-fluorouracil 500 mg/m², epirubicin 100 mg/m² and cyclophosphamide 500 mg/m²; TAC, docetaxel 75 mg/m², doxorubicin 50 mg/m² and cyclophosphamide 500 mg/m²; TCH, docetaxel 75 mg/m², cisplatin 75 mg/m² and herceptin 2 mg/kg weekly.

treatment with doxorubicin and cyclophosphamide (AC). Over 3000 women with node-positive breast cancer were randomized to either four cycles of AC followed sequentially by four cycles of paclitaxel (225 mg/m^2) or four cycles of AC alone. Tamoxifen was used in conjunction with chemotherapy in patients older than 50 years and in receptor-positive patients aged less than 50 years (Table 1).

Early results of this trial presented at the 2000 NIH Consensus Conference demonstrated no statistical benefit in disease-free or overall survival for patients receiving paclitaxel. Although, in accordance with the CALGB 9344 data, a subset analysis suggested a trend toward benefit for estrogen receptor-negative patients, the numbers did not reach statistical significance.

The CALGB 9943 and NSABP B-28 trials, both large phase III studies, contain several inherent differences that may in part explain the discordant results between them. At the outset, the baseline patient characteristics and potential baseline prognostic factors, such as age, nodal status and receptor positively, differed between the two groups. Furthermore, the sequence and schedule of drug administration as well as the number of doses of doxorubicin differed because the planned dose of paclitaxel could not be given in 25% of the NSABP group due to toxicity. Finally, when tamoxifen was started in relationship to chemotherapy differed. The accumulation of these factors complicates interpretation of the results.

The M. D. Anderson Cancer Center recently conducted a smaller phase III trial,[68] randomizing 524 women with operable breast cancer to either eight cycles of 5-FU/doxorubicin/cyclophosphamide (FAC) or four cycles of paclitaxel followed by four cycles of FAC (Table 1). This study design effectively eliminated duration of therapy as a confounding variable. At four-year follow-up, the estimated disease-free survival for all patients was 85.2% for the paclitaxel arm and 81.5% for FAC alone. The 4% risk reduction in disease-free survival in the paclitaxel arm was not statistically significant, and there was no demonstrable effect on overall survival. Preliminary data have not shown a differential relative benefit based on estrogen receptor status. Longer follow-up is needed to determine whether this trend for benefit in disease-free survival will reach statistical significance. However the small sample size may preclude the ability of this trial to show benefits gained from adding paclitaxel.

In December 1995, the NSABP initiated protocol B-27, which evaluated the sequential addition of docetaxel to anthracycline-based chemotherapy in the neoadjuvant and adjuvant settings.[69,70] In this three-arm trial, 2,411 women with operable breast cancer were randomized to receive neoadjuvant AC for four cycles followed by surgery, neoadjuvant AC for four cycles with postoperative docetaxel for four cycles, or neoadjuvant AC for four cycles followed by neoadjuvant docetaxel for four cycles (Table 1). Results of this trial presented at the San Antonio Breast Cancer Symposium in 2001 demonstrated improved clinical and pathologic response rates of approximately 22% in the arms with docetaxel.[71] The impact of docetaxel on disease-free survival and overall survival require further clinical evaluation.

Another smaller study, also presented at the 2001 San Antonio Breast Cancer Symposium, further supported the efficacy of docetaxel in the neoadjuvant setting. The Aberdeen Neoadjuvant Study evaluated 145 patients treated with four cycles CVAP. Patients responding to initial chemotherapy were randomized to four cycles of docetaxel or four more cycles of CVAP, and patients not responding to initial CVAP therapy received four cycles of docetaxel (Table 1). Patients receiving docetaxel had improved disease-free and overall survival (P = .05 and P = .03, respectively) at three years of follow-up.[72]

Paclitaxel Versus Docetaxel

No completed studies directly compare docetaxel to paclitaxel. The North American Intergroup has designed ECOG 1199 to question if either taxane is superior or shows significant differences in toxicity in the adjuvant setting. This phase III study, which has completed accrual, directly compares docetaxel and paclitaxel for adjuvant therapy of breast cancer and also addresses the optimal schedule for these agents. All patients will receive four cycles of adriamycin and cyclophosphamide (AC) followed by randomization to either four cycles of single-agent docetaxel or paclitaxel on an every three-week schedule for four cycles or a weekly schedule for 12 weeks (Table 1).

Sequential versus Combination and Dose Density

Combination therapy incorporating taxanes and anthracyclines is a topic of intense study. In the metastatic setting, both paclitaxel and docetaxel have

been studied in combination with doxorubicin, and response rates up to 94% have been reported.[73] Significant cardiac toxicities have been observed with the paclitaxel-doxorubicin combination, however,[74–76] whereas earlier results of phase I and II studies evaluating the combination of docetaxel and doxorubicin demonstrated cardiac toxicity not exceeding that found with single-agent doxorubicin.[77] Trials using paclitaxel in sequence are based on these findings, whereas docetaxel has been used both sequentially and in combination. Currently, several large phase III trials evaluating the role of adjuvant taxane-based therapy are complete, nearing completion, or underway.

Dose density is the focus of CALGB 9741, a four-arm trial that compares dose-dense (DD) therapy, sequential doxorubicin, paclitaxel, and cyclophosphamide given every two or three weeks, to a conventional schedule (CS) of AC followed by paclitaxel given every two to three weeks in women with node-positive breast cancer. The preliminary results of this study, recently reported at the 2002 San Antonio Breast Cancer Symposium, support the DD scheduling over CS with superior disease-free survival (85% vs 81%; $P = .0072$) and overall survival (92% vs 90%; $P = .014$). There was no significant difference in either DFS or OS between sequential versus combination chemotherapy.[78]

The Breast Cancer International Research Group (BCIRG) has reported the results of an adjuvant trial comparing combination docetaxel/doxorubicin/cyclophosphamide (TAC) to the established FAC regimen in node-positive patients. Preliminary results of this study from a planned interim analysis were presented at the 2002 ASCO conference. At a median 33 months of follow-up, statistically significant improvements in disease-free and overall survival with TAC over FAC ($P = .0002$ and $P = .006$, respectively) were observed. Further analysis revealed improvement in disease-free survival regardless of hormone receptor status or HER2 status.[79] Additional follow-up of the BCIRG 001 study will further clarify the efficacy of TAC compared with FAC.

A similar trial led by the North American Intergroup Association, ECOG 2197, directly compares doxorubicin and cyclophosphamide with doxorubicin plus docetaxel in 2,778 women with node-positive or high-risk node-negative breast cancer. This phase III trial, which has reached accrual, will determine whether the substitution of docetaxel for cyclophosphamide improves the classic AC regimen and will further provide valuable safety data on the AT combination in the adjuvant setting.

Several other second-generation adjuvant taxane studies are currently underway. The NSABP B-30 trial will address the issue of sequential versus concurrent polychemotherapy using docetaxel. In this study, 3,700 women with node-positive breast cancer are randomly assigned to receive four cycles of AC followed by four cycles of docetaxel, four cycles of combined doxorubicin and docetaxel, or four cycles of doxorubicin, cyclophosphamide, and docetaxel (TAC). Accrual is ongoing.

The BCIRG 005 study compliments NSABP B-30, evaluating sequential versus concurrent docetaxel in node-positive, HER2-negative patients. Similar to the NSABP study, patients are randomized to either AC for four cycles followed sequentially by four cycles of docetaxel (100 mg/m^2), or four cycles of TAC.

Future Directions

Several recently initiated clinical trials (Table 1) explore important avenues in search of the optimal adjuvant chemotherapeutic regimen using the promising improvement in OS reported with trastuzumab in patients heavily pretreated for metastatic breast cancer.[80] The North American Intergroup is conducting a trial comparing four cycles of AC followed by weekly paclitaxel to the same regimen with the addition of trastuzumab either sequentially or concomitantly. In a similar study, the NSABP is evaluating the safety and efficacy of combining taxanes with trastuzumab after four cycles of AC (NSABP B-31). Also evaluating the role of trastuzumab in combination with taxanes in the adjuvant setting, BCIRG 006 involves node-positive or high-risk node-negative patients with HER2 overexpression. It has a targeted accrual of 3,000 patients. Other trials, including the Italian Adjuvant group, the French Cooperative group, the NCCTG, and NCIC are investigating taxanes in combination with epirubicin. These promising avenues of research continue to evolve as our experience with these agents expands.

Conclusion

Despite the tremendous strides made over recent years, we continue to struggle with several unanswered issues regarding the use of taxanes in the adjuvant therapy

of breast cancer. Preliminary results from several important trials have shown small but significant and clinically important improvements in disease-free and overall survival. Perplexing questions continue to arise regarding how best to use adjuvant taxanes and which population would derive optimal benefit from these agents based on nodal status, receptor status, age, and other predictive factors. Current NCCN practice guidelines[81] support the use of adjuvant taxanes in node-positive breast cancer patients, and the November 2000 NIH Consensus Statement concurs that taxanes are appropriate in node positive patients. Pending maturation of the accumulating data, however, risk of recurrence should guide the selection of appropriate adjuvant therapy in lymph node–negative patients.[82] Clinicians and researchers alike excitedly await follow-up from ongoing landmark studies to gain a clearer understanding of the role taxanes should play in the adjuvant setting of breast cancer.

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