Taxanes in the Adjuvant Treatment of Breast Cancer: Why Not Yet?

Martine J. Piccart, Caroline Lohrisch, Luc Duchateau, Marc Buyse

The taxanes paclitaxel and docetaxel represent the most active chemotherapeutic agents developed for the treatment of advanced breast cancer in the last decade, and they are now being incorporated into adjuvant chemotherapy trials for lymph node-positive breast cancer with the hope of improving on the results achieved with CMF (cyclophosphamide, methotrexate, 5-fluorouracil) or anthracycline-based regimens. So far, three randomized paclitaxel-based adjuvant clinical trials enrolling 3170 women (Cancer and Leukemia Group B [CALGB] 9344), 3060 women (National Surgical Adjuvant Project for Breast and Bowel Cancers [NSABP]-B28), and 524 women (M. D. Anderson), respectively, have been reported with respective median follow-up times of 52, 34, and 43 months. This article critically reviews these three studies and gives an overview of the many other randomized clinical trials, due to accrue more than 17 000 women, which are investigating the potential of taxanes in adjuvant breast cancer therapy. Given that the early promise of taxanes suggested by CALGB 9344 is not yet confirmed by the two other trials, only level 2 evidence has been reached to date in regard to a positive contribution of these agents to breast cancer outcome in the adjuvant setting. It is argued that level 1 evidence is highly desirable before adopting taxane-based regimens in standard practice. It is anticipated that a meta-analysis will be needed to comprehensively define the value of taxanes in early breast cancer, and a new model of international collaboration is proposed to find a balance between the need to offer new, more effective therapies to patients as soon as possible and the danger of drawing wrong, premature conclusions regarding the magnitude of benefit of a new regimen. [J Natl Cancer Inst Monogr 2000;30:88–95]

INTRODUCTION

Adjuvant chemotherapy with CMF (cyclophosphamide, methotrexate, 5 fluorouracil) and anthracycline-based regimens is associated with significant reductions in breast cancer mortality (1). Research efforts have explored numerous treatment strategies in attempts to further improve survival, including the addition of newer anticancer drugs that have demonstrated activity in the metastatic setting, such as the taxanes. Paclitaxel (Taxol, Bristol-Myers Squibb, Princeton, NJ) and docetaxel (Taxotere; Aventis, Collegeville, PA) undoubtedly represent the most active chemotherapeutic agents developed in the last decade for the treatment of advanced breast cancer. Outstanding features of these agents that have been the focus of several reviews (2–5) include, first, their original mechanism of action, namely, binding to and stabilization of microtubules, thereby preventing their depolymerization; second, their partial lack of cross-resistance with anthracyclines, to which they compare favorably as far as single-agent activity; and third, their capacity to be combined with almost all active chemotherapeutic agents commonly used for breast cancer therapy.

The next logical step in the clinical development of the taxanes was their incorporation into adjuvant chemotherapy regimens for lymph node-positive breast cancer with the hope of extending disease-free survival and overall survival.

The oldest of the two compounds, paclitaxel, was the first to enter the adjuvant scene; as a result, only paclitaxel-based adjuvant clinical trials have been reported to date. Fig. 1 summarizes the chronology of those reports and their affect on regulatory agencies in the United States (U.S. Food and Drug Administration [FDA]) and in Europe (European Medical Agency [EMEA]).

The large U.S. Intergroup trial, referred to as Cancer and Leukemia Group B (CALGB) 9344, explored the value of adding four cycles of paclitaxel to four cycles of AC (doxorubicin–cyclophosphamide) as postoperative adjuvant therapy of lymph node-positive breast cancer in 3170 women. This trial, in fact, had a 3 × 2 factorial design to compare three doses of doxorubicin (60, 75, or 90 mg/m² by random allocation) plus cyclophosphamide (600 mg/m²) given intravenously on day 1 every 3 weeks for four courses (AC × 4), and then, second, to compare paclitaxel at a dose of 175 mg/m² as a 3-hour infusion every 3 weeks given for four courses following AC (AC/T) versus no additional chemotherapy. The superior results of the paclitaxel arm were reported at its first planned interim analysis, conducted at a median follow-up time of 20 months, and were presented at the 1998 meeting of the American Society of Clinical Oncology (ASCO) (6); an update with a median follow-up of 30 months was presented to the ODAC (Oncology Drug Advisory Committee) with subsequent registration of the paclitaxel-based adjuvant regimen for lymph node-positive disease by the FDA in late 1999.

In contrast, in March 2000, the European Regulatory Agency, provided with the same set of data (7), viewed these data as “premature” and did not license paclitaxel for adjuvant use in the European Union. Since then, two other paclitaxel-based adjuvant breast cancer trials have been reported with inconclusive results: the relatively small M. D. Anderson trial presented at the 2000 meeting of ASCO (8) and the large National Surgical Adjuvant Project for Breast and Bowel Cancers (NSABP)-B28 trial presented at the November 2000 NIH Breast Cancer Consensus Conference (9).

In the former trial, women were randomly assigned to receive either eight cycles of FAC (5-fluorouracil, doxorubicin, and cy-


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clophosphamide) or four cycles of paclitaxel followed by four cycles of FAC, with a proportion of patients receiving some of the chemotherapy preoperatively. Although there was a 24% risk reduction for recurrence in the group treated with paclitaxel, this was not significant, given the short follow-up and small trial size. No difference in overall survival was observed between the two groups.

The NSABP-B28 trial, conducted in 3060 women with lymph node-positive breast cancer, adopted a very similar design to the one of CALGB 9344, with four cycles of AC being compared with four cycles of AC followed by four cycles of paclitaxel, whereas the former trial randomly assigned 524 patients to eight cycles of FAC or four cycles of paclitaxel followed by four cycles of FAC.

In this article, we carefully review the available evidence that led us to conclude that taxane-based regimens cannot at present be recommended as gold-standard adjuvant chemotherapy for women with invasive breast cancer.

SIMILARITIES AND DIFFERENCES BETWEEN THE THREE REPORTED PACLITAXEL TRIALS: CALGB 9344, M. D. ANDERSON, AND NSABP-B28

Treatment Differences

Both CALGB 9344 and NSABP-B28 opted for a relatively short anthracycline-based control arm (four cycles of AC), whereas the M. D. Anderson trial chose eight cycles of FAC as control. The dose and sequence of chemotherapy regimens varied in the three trials: Only CALBG 9344 intensified the dose per cycle of anthracycline compared with a standard AC, keeping the total number of cycles at four. The NSABP-B28 study used a standard AC regimen with respect to anthracycline dose but gave a higher paclitaxel dose: 225 mg/m², as opposed to 175 mg/m² in CALGB 9344. In the M. D. Anderson trial, paclitaxel was given before anthracyclines and as a 24-hour infusion, and the anthracycline regimen consisted of eight cycles in the control arm, compared with four cycles in both CALBG 9344 and NSABP-B28. This last trial was the only one of the three trials to have the same total number of cycles in both the paclitaxel and nonpaclitaxel arms.

Also, while patients in both CALGB 9344 and NSABP-B28 received all chemotherapy postoperatively, this was only the case in two-thirds of the patients in the M. D. Anderson trial; the remainder received four courses before and four courses after primary surgery.

All three trials planned adjuvant tamoxifen therapy for patients with hormone-sensitive tumors, defined as those having estrogen receptor (ER)-positive and/or progesterone receptor (PgR)-positive tumors. In addition, all women more than 50 years old were given adjuvant tamoxifen in NSABP-B28 irrespective of their hormone receptor status. As a result of these different criteria, 85% of the women received tamoxifen in NSABP-B28, compared with only 70% in CALGB 9344.

Finally, the timing of adjuvant tamoxifen differed: It was given at completion of chemotherapy in the CALGB and M. D. Anderson studies but given concomitantly with chemotherapy in NSABP-B28.

Patient Population Differences

It is worth noting that CALGB 9344 enrolled patients at a higher risk of relapse than did NSABP-B28: Slightly more than half of the trial population had four or more positive axillary lymph nodes in the former, as compared with approximately one-third in the latter (6).

In the M. D. Anderson trial, the proportion of patients with zero, one to three, and four or more positive lymph nodes was approximately one third each (8).

Finally, NSABP-B28 seems to have recruited a somewhat older patient population, with 51% of the women being under the age of 50 years, compared with 56% of the women being under 50 years of age in the M. D. Anderson trial and a total of 62% premenopausal women in CALGB 9344. The NSABP trial also had the highest rate of hormone receptor-positive tumors (66% versus 58% in the two other studies) (9).
Outcome of the Trials

CALGB 9344 is now quite mature, with a median follow-up of 52 months and 901 events, including 589 deaths. As with its first planned interim analysis (presented in May 1998 after the occurrence of 453 events) and its second unplanned interim analysis (presented at the FDA in September 1999 with 624 events), results continue to show both disease-free and overall survival advantages for the AC/T arm, with a relative risk reduction for recurrence of 13% and for death of 14% compared with the AC-alone arm (10). This trend toward decreased mortality in the AC/T compared with AC arms no longer reaches statistical significance, although the disease-free survival remains significantly better for AC/T. A possible explanation is the emergence of late recurrences: The addition of paclitaxel may have reduced early recurrences in aggressive tumors, for which four cycles of AC were inadequate, but a second peak of late recurrences of these and of less aggressive tumors, on which the addition of paclitaxel did not have a major effect, is resulting in a narrowing of the treatment effect for AC/T.

The small M. D. Anderson trial, with 75 events and 28 deaths, does not show an advantage for the paclitaxel arm at a median follow-up of 43 months.

The third interim analysis of the NSABP-B28 trial, with 551 events and 269 deaths, does not show a difference either, with a median follow-up of 34 months (the first two interim analyses were not reported since they showed no significant treatment effect). The estimated overall survival at 36 months is 92% for the AC arm and 90% for the AC/T arm; estimated disease-free survival at 36 months is 81% in both arms (9).

Discussion

Weaknesses of CALGB 9344

The CALGB 9344 trial has design limitations, and it is unclear to what extent these explain the apparent paclitaxel effect. A major potential confounder in this trial is the duration of therapy, which is longer in the paclitaxel-containing arm by 12 weeks (four cycles of cytotoxic therapy). This issue represents a difficult puzzle because the trials available to date do not adequately answer the question of the relative importance of total duration of therapy and cumulative dose.

The Oxford overview reported that anthracycline-based therapy may be associated with a small survival advantage over CAF (1). Whereas studies (6,11,12) have failed to demonstrate that intensification beyond a threshold dose intensity improves survival, below that threshold there does seem to be a dose–response relationship, with a compromised outcome (13,14). Thus, we are faced with the question of whether the cumulative dose of doxorubicin (A) in four cycles of AC (240 mg/m²) is below this threshold, rendering it equally effective to CAF and less effective than it could be. If the answer is yes, it may explain the apparent discrepancy in the results of NSABP-B15 (equivalence for six cycles of CMF and four cycles of AC 240 mg/m² doxorubicin total dose), the National Cancer Institute of Canada comparison of CEF (cyclophosphamide, epirubicin, 5-fluorouracil) and CMF (CEF 7% superior overall survival, 720 mg/m² epirubicin total dose), and the Intergroup trial (INT 0102) of CAF (cyclophosphamide, Adriamycin, 5-fluorouracil) versus CMF (CAF 2% superior overall survival) (15–17). Indeed, although four cycles of AC (doxorubicin at 60 mg/m² per cycle) is a standard adjuvant regimen in North America, many European and Canadian oncologists give several cycles of CMF following four cycles of AC or four cycles of A or a higher total dose of anthracyclines, such as can be found in CAF/FAC and CEF/FEC regimens.

In the case of this study, both the different duration of chemotherapy in the paclitaxel and nonpaclitaxel arms and the potentially inadequate (or suboptimal) anthracycline cumulative dose in one-third of the patients treated in the control arm may have biased the results in favor of the AC/T arm.

Table 1 summarizes the few randomized trials that have compared 6 months of CMF with 3 months of CMF or 6 cycles of anthracycline-based therapy with three cycles of anthracycline-based therapy in operable breast cancer patients with positive axillary lymph nodes.

The first two trials (18,19), described in Table 1, were conducted in Germany, enrolled a majority of postmenopausal women, and used an intravenous day 1 + 8 CMF regimen. Each accrued fewer than 1000 women and failed to detect an advan-

<table>
<thead>
<tr>
<th>Group (reference No.)</th>
<th>Comparison</th>
<th>No. of eligible patients</th>
<th>Patients who are estrogen receptor negative, %</th>
<th>Patients who are premenopausal or aged &lt;50 y, %</th>
<th>Follow-up, y</th>
<th>Results, DFS (HR longer vs. shorter)</th>
<th>Results, OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>GBSG (18)</td>
<td>6 CMF (iv d 1 + 8)</td>
<td>473</td>
<td>30</td>
<td>42</td>
<td>9</td>
<td>0.95</td>
<td>95% CI = 0.74 to 1.2</td>
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<tr>
<td></td>
<td>3 CMF ± tamoxifen</td>
<td></td>
<td></td>
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<td></td>
<td>No difference (P = .34)</td>
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<tr>
<td>GABG (ASCO) (19)</td>
<td>6 CMF (iv d 1 + 8)</td>
<td>789</td>
<td>66</td>
<td>15</td>
<td>3</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>3 CMF</td>
<td></td>
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<tr>
<td>IBCSG (VI) (20)</td>
<td>6 CMF</td>
<td>1475</td>
<td>30</td>
<td>100</td>
<td>5</td>
<td>58</td>
<td>53</td>
</tr>
<tr>
<td></td>
<td>3 CMF ± reintroduction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(P = .01) (P = .06)</td>
<td></td>
</tr>
<tr>
<td>FASG (ASCO) (21)</td>
<td>6 FE (50) C</td>
<td>602</td>
<td>27</td>
<td>100</td>
<td>8</td>
<td>55</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td>5 FE (50) C</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(P = .01) (P = .06)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 FE (75) C</td>
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</table>

*GBSG = German Breast Cancer Study Group; GABG = German Adjuvant Breast Cancer Study Group; IBCSG = International Breast Cancer Study Group; FASG = French Adjuvant Study Group; ASCO = American Society of Clinical Oncology; C = cyclophosphamide; E = epidoxorubicin; F = 5-fluorouracil; M = methotrexate; CI = confidence interval; DFS = disease-free survival; HR = hazard ratio; OS = overall survival; iv = intravenous; d = day. 
†122 patients excluded as ineligible.
tage for the longer CMF treatment at median follow-up times of 9 and 3 years, respectively.

In contrast, the larger IBCSG (International Breast Cancer Study Group) trial VI (20) used the classic oral CMF regimen and targeted exclusively premenopausal women, one-third of whom had ER-negative tumors. At a median follow-up of 5 years, disease-free-survival, but not overall survival, was significantly better for the 6-month CMF arm than for the 3-month CMF arm, with a subset analysis suggesting that this benefit was more evident for younger women (aged <40 years) and for those with ER-negative tumors.

The last study, conducted in France, also focused exclusively on premenopausal women, comparing six cycles of FEC given once every 3 weeks (5-fluorouracil, epirubicin at a dose of 50 mg/m2, and cyclophosphamide) with three cycles of either the same regimen or a regimen with a somewhat higher dose of epirubicin (75 mg/m2). The results of this trial, recently updated with an 8-year median follow-up (21), show that six cycles of FEC are superior to three cycles of FEC as far as disease-free survival, with a similar trend for overall survival. The weakness here is the suboptimal epirubicin dose per cycle, which prohibits comparison of these data to those obtained using adequately dosed anthracycline-based regimens.

We can tentatively draw three conclusions: 1) that the issue of the optimal duration of adjuvant chemotherapy has not been adequately studied; 2) that two clinical trials targeting premenopausal, lymph node-positive breast cancer patients have shown that 3 months or three cycles of adjuvant chemotherapy are inferior to 6 months or six cycles of adjuvant chemotherapy; and 3) that a subset analysis in one of these trials suggests that the ER-negative tumors benefit from longer treatment.

These three conclusions raise the concern that an increased duration of chemotherapy for an ER-negative population, in particular, may have contributed to the paclitaxel effect, a concern that is reinforced by the results of a subset analysis of CALGB 9344, which strongly suggests that only patients with hormone receptor (HR)-negative tumors (one-third of the study population) benefit from the addition of paclitaxel.

For the 2066 HR-positive patients, the hazard ratio for recurrence was 0.92 (95% confidence interval [CI] = 0.73 to 1.16) for AC/T versus AC, whereas for HR-negative patients, it was 0.68 (95% CI = 0.55 to 0.85) (7). A similar trend was observed in the M. D. Anderson trial: 58% of the population was HR positive, and although not statistically significant, the absolute difference in disease-free survival for FAC versus paclitaxel/FAC was 3% for HR-positive patients and 5% for HR-negative patients.

There are several potential explanations for the lower event rate in the AC/T arm to date: First, the baseline risk for patients with HR-positive tumors is lower and, therefore, a benefit of paclitaxel is more difficult to demonstrate, particularly if it is small; or, second, the baseline risk of HR-positive patients is sufficiently lowered by AC and tamoxifen that the added benefit of paclitaxel, if it exists, cannot be demonstrated with this sample size and follow-up period; or, third, recurrences in the HR-positive population occur later and a benefit may still become apparent with longer follow-up.

In the NSABP-B28 trial, a subset analysis did not suggest a clear benefit of adding paclitaxel in the small subset of patients who did not receive tamoxifen (9). Given the apparent relationship between HR status and benefit suggested by the CALGB 9344 and M. D. Anderson trials, an analysis according to ER status would be of interest in this trial, as well.

It is important, however, to remember that subset analyses are dangerous and potentially misleading: The trials that have compared 5-fluorouracil plus levamisole with no chemotherapy in colorectal cancer nicely illustrate how two trials of similar design and similar size can draw opposite conclusions as to who benefits, based on subset analysis.

The trial by Moertel and colleagues (22,23) concluded that the regimen was effective in Dukes’ C but not Dukes’ B colorectal cancer, while the one by Zoetmulder et al. (24) stated that the therapy provided benefit to Dukes’ C and B colon cancer patients but not to those with rectal cancer.

Nevertheless, subset analyses generate interesting hypotheses, and the CALGB 9344 analysis by ER status, even if unplanned a priori, raises awareness about potential population differences in the magnitude of the taxane benefit, if such a benefit can be confirmed by other trials. In any event, these analyses support the contention that we cannot make sweeping generalizations about the value of adjuvant paclitaxel on the strength of the available evidence.

Table 2 illustrates the design of four trials ready to start or still being discussed in Europe and/or Canada that challenge CALGB 9344 on several important issues: first, a potentially improved anthracycline-based control arm given for 6 months (MA21 trial, U.K. trial); second, a dose-dense epirubicin–cyclophosphamide (MA-21 trial) or an individually “targeted” FEC regimen (Scandinavian trial) as opposed to higher fixed doses of doxorubicin given in combination with cyclophosphamide every 3 weeks (CALGB 9344); third, other nontaxane sequential regimens following four epirubicin cycles (U.K. trial); and, last but not least, the key issue of which subset of patients might derive the greatest benefit from adjuvant taxane-based therapy (Breast International Group [BIG]-01-00 study).

This last trial, to be coordinated by the EORTC (European Organization for Research and Treatment of Cancer) under the umbrella of the BIG (25), is a trial of considerable interest today, given the present confusion regarding the role of the taxanes in adjuvant breast cancer therapy. It is powered to test a biologic hypothesis, namely, that the benefit of taxanes might be confined largely to the subgroup of patients with p53-mutated tumors. This hypothesis has more support from laboratory data than the one relating taxane benefit to hormonal receptor status (26–33). Eligibility requirements for this trial include availability of an adequate tumor biopsy, part of which will be snap-frozen and processed for a p53 functional yeast assay and for microarray analysis.

The last concern raised by CALGB 9344, before the third analysis presented by C. Henderson, is the appropriateness of presenting positive interim results early, especially if the level of significance is not corrected for the fact that they are interim analyses. The initial results were reported less than 1 year after the accrual of the last patient (3-year accrual period) based on a preplanned interim analysis at the time of 450 events. One cannot extrapolate these significant results to later points in time unless one assumes a constant hazard ratio over time (proportional hazards model). Given that there appear to be two peaks of breast cancer recurrence, at 2 and 5 years, it is likely that this assumption is incorrect.

Clinical trial statisticians today perform planned interim analysis based on a precalculated number of events, as this tech-
the case for adjuvant paclitaxel, which means that we are left
with the unexplained story of paclitaxel in the front-line treatment of advanced epithelial ovarian cancer is worth summarizing here because it illustrates this confusion particularly well. Two consecutive randomized clinical trials—the GOG (Gynecologic Oncology Group) #111 trial and the European-Canadian intergroup trial—addressing the question of a potential superiority of a paclitaxel–cisplatin regimen over a cyclophosphamide–cisplatin regimen showed remarkable similarities in outcome, making the medical community on both sides of the Atlantic confident that a new gold-standard chemotherapy regimen, namely paclitaxel–cisplatin, was born in the year 2000 (39,40). Unfortunately, a few months later, the results of a much larger multicenter trial, both with one large positive trial showing divergent effect across HR subpopulations and with two inconclusive trials.

**Balancing New Effective Therapies With Premature Reporting of Their Potential Benefits**

A balance is needed between being able to offer new effective therapies as soon as possible and the danger of presenting premature and possibly incorrect conclusions about the magnitude of benefit of such new therapies. At present, we have only reached level 2—evidence that taxanes contribute some additional benefit in breast cancer adjuvant therapy, given one positive trial and two inconclusive ones (Table 3) (38). Level 1 evidence is highly desirable for reaching a consensus worldwide but is unlikely to be obtained without a meta-analysis, given the high probability that some trials will show an effect and others will not.

Changing clinical practice on the basis of one trial causes confusion and can be detrimental when subsequent trials fail to confirm the findings of the first. The surprising and as yet unexplained story of paclitaxel in the front-line treatment of advanced epithelial ovarian cancer is worth summarizing here because it illustrates this confusion particularly well. Two consecutive randomized clinical trials—the GOG (Gynecologic Oncology Group) #111 trial and the European-Canadian intergroup trial—addressing the question of a potential superiority of a paclitaxel–cisplatin regimen over a cyclophosphamide–cisplatin regimen showed remarkable similarities in outcome, making the medical community on both sides of the Atlantic confident that a new gold-standard chemotherapy regimen, namely paclitaxel–cisplatin, was born in the year 2000 (39,40). Unfortunately, a few months later, the results of a much larger multicenter trial,

### Table 2. Planned or ongoing randomized clinical trials that challenge Cancer and Leukemia Group B 9344*

<table>
<thead>
<tr>
<th>Group</th>
<th>Trial</th>
<th>Trial design</th>
<th>Comments</th>
</tr>
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<tbody>
<tr>
<td>NCI-C-CTG</td>
<td>MA-21</td>
<td>6 CEF (Canadian)</td>
<td>Same treatment duration in all three arms</td>
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<tr>
<td></td>
<td></td>
<td>4 AC → 4 P</td>
<td>Hypothesis: I = II, III&gt;II, or II</td>
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<tr>
<td></td>
<td></td>
<td>Dose-dense 6 EC → 4 P + G-CSF + erythropoetin</td>
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<tr>
<td>UK-CRC</td>
<td>TACT</td>
<td>8 FEC</td>
<td>Same treatment duration in all three arms</td>
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<tr>
<td></td>
<td></td>
<td>4 FEC → 4 D</td>
<td>Trial still under discussion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4 E → 4 CMF</td>
<td></td>
</tr>
<tr>
<td>Scandinavian trial</td>
<td>SBG01-XX</td>
<td>8 Tailored FEC</td>
<td>Tailored FEC means increasing doses in the individual patient up to a</td>
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<tr>
<td></td>
<td></td>
<td>4 AC → 4 P</td>
<td>target degree of myelosuppression</td>
</tr>
<tr>
<td>BIG (coordinated by EORTC)</td>
<td>BIG 01-00</td>
<td>FEC or Canadian CEF (preop)</td>
<td>Hypothesis: D increases disease-free survival by 20% in p53+ tumors</td>
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<tr>
<td></td>
<td></td>
<td>3 D → 3 EC</td>
<td>but only by 5% in p53− tumors</td>
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<tr>
<td></td>
<td></td>
<td>Frozen biopsy for p53</td>
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<td></td>
<td></td>
<td>analysis mandatory</td>
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</table>

*NCI-C-CTG = National Cancer Institute of Canada Clinical Trials Group; UK-CRC = United Kingdom-Cancer Research Campaign; BIG = Breast International Group; EORTC = European Organization for Research and Treatment of Cancer; A = adriamycin; C = cyclophosphamide; D = docetaxel; E = epirubicin; F = 5-fluorouracil; M = methotrexate; P = paclitaxel; G-CSF = granulocyte colony-stimulating factor; Preop = preoperatively; Dose-dense = every 2 weeks; Canadian CEF = cyclophosphamide 75 mg/m² orally for 14 days, epirubicin 60 mg/m² intravenously day 1+8, 5-fluorouracil 500 mg/m² intravenously day 1+8, administered every 4 weeks with prophylactic antibiotics.

**Are the M. D. Anderson and the NSABP-B28 Trials Negative Trials?**

The M. D. Anderson and NSABP-B28 trials are still compatible with a small absolute benefit from adjuvant paclitaxel (perhaps a 1%–2% gain in overall survival) that may be presently undetectable but that could emerge with longer follow-up. This is a reasonable assumption for NSABP-B28 because this trial has many patients and, therefore, has adequate power to detect a small but clinically relevant benefit. The M. D. Anderson trial, however, is a smallish trial for this adjuvant setting and, therefore, will only ever show significance for a large treatment benefit.

Therefore, these two trials presently neither help nor hinder the case for adjuvant paclitaxel, which means that we are left both with one large positive trial showing divergent effect across HR subpopulations and with two inconclusive trials.

**Balancing New Effective Therapies With Premature Reporting of Their Potential Benefits**

A balance is needed between being able to offer new effective therapies as soon as possible and the danger of presenting premature and possibly incorrect conclusions about the magnitude of benefit of such new therapies. At present, we have only reached level 2—evidence that taxanes contribute some additional benefit in breast cancer adjuvant therapy, given one positive trial and two inconclusive ones (Table 3) (38). Level 1 evidence is highly desirable for reaching a consensus worldwide but is unlikely to be obtained without a meta-analysis, given the high probability that some trials will show an effect and others will not.

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### Table 3. Types of evidence levels that form the basis of treatment options

<table>
<thead>
<tr>
<th>Evidence level</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>Level 1 evidence</td>
<td>More than one consistent randomized clinical trial and/or meta-analysis</td>
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<tr>
<td>Level 2 evidence</td>
<td>One or a few unconfirmed randomized trials or more randomized trials with conflicting results</td>
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<tr>
<td>Level 3 evidence</td>
<td>Evidence from nonrandomized trial with reliable external control</td>
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</table>
the Third International Collaborative Ovarian Neoplasm Study (ICON3), comparing carboplatin–paclitaxel with carboplatin or CAP (cyclophosphamide, doxorubicin, cisplatin) were presented along with a 29-month median follow-up and showed no apparent overall advantage for the paclitaxel-containing arm (41). It is unclear whether the disappointing ICON3 results will change with a longer follow-up, but they certainly call for a meta-analysis of all trials, published or not, that have looked at potential improvement from taxane incorporation into first-line chemotherapy for epithelial ovarian cancer.

Fig. 2 summarizes all reported and unreported taxane adjuvant breast cancer trials in the world (42) and shows the huge imbalance between the reported trials, which have enrolled 6754 women, and the unreported ones, which are accruing about 17,854 women. Among the latter, four trials that are all exploring the potential benefit of adjuvant docetaxel (Taxotere) are already closed: They have accrued 8700 women. The remaining seven trials, which explore the potential benefits of either paclitaxel or docetaxel, are ongoing with a planned total enrollment of 9150 women. Waiting until these trials are completed and published before conducting a first meta-analysis would mean a long delay before settling the question of the effect of adjuvant taxanes.

In an ideal world, one could envisage setting up a large, independent meta-analysis unit that would have the capacity to respond to today’s rapid acceleration of adjuvant trials conducted across continents. If it were provided with data on events occurring in all recently closed trials, examining a similar question (in our case, the taxane contribution to outcome in adjuvant breast cancer therapy) at regular intervals, the magnitude of therapeutic effect of the test question could be estimated earlier and with more precision.

This model, illustrated in Fig. 3, is very challenging because it implies strong collaboration between groups involved in trials of adjuvant therapy as well as mutual trust and close contact with independent statisticians. It could be designed in a way that would prevent any public disclosure of individual trial results, the main emphasis being the periodic evaluation of the overall treatment effect and its statistical reliability. Such a model would probably represent a gain of several years in reaching enough confidence in the contribution of a particular agent or regimen to improved patient outcome. It is, therefore, a desirable model and places the interest of patients above the interests of investigators or the pharmaceutical industry.

The Future of Adjuvant Taxane-Based Therapy

With more than 20,000 women enrolled in trials exploring the potential benefit of taxane incorporation into adjuvant chemotherapy programs (42), one can be confident that their potential contribution to improved survival, even if modest, will be identified by a well-conducted overview. This overview should explore differential treatment effects in different patient subsets, defined by treatment, patient, or even tumor molecular marker characteristics whenever available.

Regarding treatment strategies, it is important to acknowledge that, thus far, available data have come only from trials giving paclitaxel- and anthracycline-based combinations in sequence. Table 4 shows that at least seven trials are exploring the potential added value of taxanes given in combina-

![Fig. 2. Taxane-based adjuvant breast cancer trials worldwide. Taxol = paclitaxel; CALGB 9344 = Cancer and Leukemia Group B; NSABP-B28 = National Surgical Adjuvant Breast and Bowel Project; ECTO = European Cooperative Trial in Operable Breast Cancer; MIG-5 = Gruppo Oncologico Nord Ovest; Taxotere = docetaxel; ECOG = Eastern Cooperative Oncology Group; FNCLCC = Fédération Nationale des Centres de Lutte contre le cancer; BIG = Breast International Group; ANGLO CELTIC = Anglo Celtic group; GEICAM = Grupo Espanol de Investigacion en Cancer de Mama; ICCG = International Collaborative Cancer Group.](image-url)
tion with anthracyclines. One trial, BIG 2-98, is directly comparing the combination strategy; in this case, it is docetaxel combined with doxorubicin, with the sequential strategy, namely, single-agent docetaxel following single-agent doxorubicin (42).

It is very rewarding to see the tremendous international collaboration that is making these large trials possible. Let us hope that the learning curve in the conduct of these intergroup trials will soon be accompanied by innovative and creative ways to more rapidly and more efficiently collect and analyze the data these trials are generating.

REFERENCES


(7) Taxol (paclitaxel) scientific package insert; summary of product characteristics, Bristol-Myers Squibb, Wallingford, CT.


Fig. 3. Adjuvant breast cancer therapy in an ideal world. Trials 1 to 5 = Trials investigating a similar question, closed to patient entry.

Table 4. Complementary designs of taxane-based adjuvant breast cancer trials worldwide*

<table>
<thead>
<tr>
<th>Taxanes in combination (no asymmetry in duration)</th>
<th>Taxanes in sequence (no asymmetry in duration)</th>
<th>Sequence or combination: which is best?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taxol 4 ET vs. 6 CEF (MIG-5)</td>
<td>8 ET vs. 4 EC → 4 T</td>
<td></td>
</tr>
<tr>
<td>4 AT → 4 CMF vs. 4 A → 4 CMF (ECTO)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taxotere TAC vs. FAC (TAX316, GEICAM)</td>
<td>3 FEC → 3 T vs. 6 FEC (FNCLCC)</td>
<td></td>
</tr>
<tr>
<td>3 ET → 4 CMF vs. 3 A → 4 CMF vs. 4</td>
<td>4 A → 3 CMF vs. 3 A → 3 T → 3 CMF vs. 4</td>
<td></td>
</tr>
<tr>
<td>AT vs. AC (ECOG, ANGLO-CELTIC)</td>
<td>AT → 3 CMF vs. 4 AC → 3 CMF (BIG 2-98)</td>
<td></td>
</tr>
<tr>
<td>3 E d1 + 8 → 3 T vs. E 6 d1 + 8 (ICCG)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


(41) Harper P, on behalf of the ICON Collaborators. Cancer Division, MRC Clinical Trials Unit. A randomized comparison of paclitaxel (T) and carboplatin (J) versus a control arm of single agent carboplatin (J) or CAP (cyclophosphamide, doxorubicin and cisplatin): 2075 patients randomised into the 3rd International Collaborative Ovarian Neoplasm Study (ICON3) [abstract]. Proc ASCO 1999;18:1375.