Anthracyclines and taxanes in the neo/adjuvant treatment of breast cancer: does the sequence matter?

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Background: In early breast cancer, adjuvant chemotherapy decreases the risks of recurrence and breast cancer mortality, and neoadjuvant treatment leads to equivalent long-term outcomes. A large number of clinical trials have attempted to refine systemic therapeutic strategies in early breast cancer, but little attention has been paid to the sequence of anthracyclines and taxanes. Based on preclinical observations, there is limited rationale to administer the taxane before the anthracycline.

Methods: We searched PubMed, the American Society of Clinical Oncology website, and clinicaltrials.gov with the goal of identifying published or ongoing studies that aimed at comparing reverse sequences of anthracyclines and taxanes. Given the nature and the small number of studies identified, we did not attempt to quantitatively pool the study results.

Results: We retrieved seven studies in the adjuvant setting and eight in the neoadjuvant setting: 10 randomized trials (only 2 were phase III), 3 retrospective studies, and 2 ongoing phase II trials. A total of nearly 5000 patients were included in such studies. None of the clinical trials has shown disadvantages in terms of efficacy or toxicity for sequences in which the taxane was administered first. In the neoadjuvant setting, studies have collectively shown similar or increased pathological complete response rates for sequences in which the taxane was administered first.

Conclusion: Given the available information, there seems to be sufficient evidence to suggest that a taxane followed by an anthracycline is a sequence option that can be incorporated into daily clinical practice.

Key words: anthracyclines, breast neoplasms, chemotherapy, adjuvant, drug therapy, toxoids

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**Methods**

We searched PubMed, the American Society of Clinical Oncology (ASCO) website, and the National Cancer Institute’s trials registry (clinicaltrials.gov) with the goal of identifying published or ongoing clinical trials or retrospective studies that aimed at comparing reverse sequences of anthracyclines and taxanes in at least two of the study arms. We conducted PubMed searches using the Medical Subject Headings or search terms ‘breast neoplasms’, ‘chemotherapy’, ‘adjuvant’, ‘neoadjuvant’, ‘anthracyclines’, ‘taxanes’, ‘docetaxel’, ‘doxorubicin’, ‘epirubicin’, and ‘paclitaxel’, with no limitation of language, publication date, or journal of publication. One thousand three hundred four potential studies were identified in PubMed, but only nine were eligible according to our criteria. We searched available abstracts from ASCO Annual Meetings 2000 through 2013 and that search yielded two trials. Three hundred ninety-two breast-cancer trials were identified in the clinicaltrials.gov database, but only two ongoing trials addressed anthracycline and taxane sequencing in nonmetastatic breast cancer. In addition to those three databases, we also considered studies known to us, which led to one additional study (with an adjuvant and a neoadjuvant component) presented at the San Antonio Breast Cancer Symposium. Given the small number of studies identified, the fact that some are retrospective studies, the limited number of patients enrolled, and the differences between the clinical trials, we did not attempt to quantitatively pool the study results, which are therefore presented in a descriptive form according to treatment setting (adjuvant and neoadjuvant).

**Results**

**Adjuvant Studies**

Table 1 presents summary information on the seven studies in the adjuvant setting that we identified in our search: five were randomized phase II trials, one was a retrospective study, and one is still ongoing. The largest of the adjuvant studies is a still unpublished retrospective analysis of 1596 patients in the breast cancer adjuvant cohort from the M.D. Anderson Cancer Center [16]. The analysis of this cohort showed that the sequence in which the anthracycline was followed by the taxane was associated with a significantly higher risk of death (HR = 2.02; P = 0.001) but not of relapse (HR = 1.21; P = 0.33), when compared with the reverse sequence, after stratification for age, hormone-receptor status, and HER-2 status.

Cardoso et al. [17] treated two consecutive groups of patients with operable, node-positive breast cancer with either doxorubicin for three cycles, followed by docetaxel for three cycles, followed by i.v. CMF for three cycles (n = 20) or docetaxel for three cycles, followed by doxorubicin for three cycles, followed by ‘oral CMF’ for three cycles (n = 14). The median relative dose intensity (RDI) was 100% for doxorubicin and docetaxel in both groups of patients. Due to the small number of patients, no conclusion could be drawn regarding the most tolerable or most effective adjuvant regimen in that nonrandomized study.

Piedbois et al. [18] randomly assigned 99 patients with node-positive breast cancer to receive one of three adjuvant regimens: a standard-dose regimen of docetaxel, epirubicin, and cyclophosphamide for six cycles; epirubicin and cyclophosphamide for four cycles, followed by docetaxel for four cycles; or docetaxel for four cycles, followed by epirubicin and cyclophosphamide for four cycles; the latter two regimens were administered every 2 weeks with pegfilgrastim support. The primary objective of this phase II trial was to assess safety with the two dose-dense regimens, which yielded more frequent and severe nonhematological toxicity than the standard-dose regimen. When the two dose-dense regimens were compared (n = 65), neutropenia and mucositis were more frequent when the anthracycline was given first, despite similar RDIs for epirubicin and cyclophosphamide in both arms and lower RDI for docetaxel in the arm treated with anthracycline first. The authors concluded that the observed rates of grade 3 and 4 adverse events make it difficult to recommend either dose-dense regimen for further investigation. No efficacy results were reported.

Fifty-six patients with node-positive breast cancer were randomly assigned by Puhalla et al. [19] to one of two dose-dense regimens: docetaxel for four cycles followed by doxorubicin and cyclophosphamide for four cycles; or to the reverse sequence in identical doses and schedule. Pegfilgrastim was administered in all treatment cycles, and the primary hypothesis was that the administration of the taxane first would be more tolerable. Dose-dense docetaxel followed by doxorubicin and cyclophosphamide led to fewer dose reductions (46% versus 18%) and a higher RDI for docetaxel than the reverse sequence, with similar RDIs for doxorubicin and cyclophosphamide in both arms. The authors concluded that larger trials of docetaxel before anthracyclines are justified, but no efficacy results were presented.

In a randomized phase II trial with a two-by-two factorial design, Wildiers et al. [20] assessed the role of anthracycline and taxane sequence, as well as the role of dose-density, in the tolerability and delivery of adjuvant therapy to patients with high-risk breast cancer. The 117 patients were randomized to one of four treatment arms: three cycles of conventional fluorouracil, epirubicin, and cyclophosphamide (FEC), followed by three cycles of conventional docetaxel; the reverse sequence; a dose-dense regimen of FEC every 10–11 days for four cycles, followed by four cycles of docetaxel every 2 weeks; or the reverse, dose-dense sequence. Pegfilgrastim was given as a single injection on day 2 of each cycle as primary prophylaxis in dose-dense arms, and as secondary prophylaxis in conventional-dose arms. Significantly fewer dose delays occurred in patients who received docetaxel before the anthracycline-based regimens (5% versus 17%). There was also a suggestion that prior administration of anthracyclines increases the skin toxicity of docetaxel, while the alternative sequence led to more myalgia.

In a more recent trial from Japan, 42 patients with node-positive or high-risk, node-negative breast were randomized to a conventional sequence of three cycles of FEC, followed by three cycles of docetaxel, all administered every 3 weeks, or the reverse sequence, in which identical doses and schedule were used [21]. The overall RDI for epirubicin and for docetaxel was similar in both arms; however, there was more grade 3/4 febrile neutropenia, anorexia, nausea, and vomiting in the arm with the anthracycline first, whereas the reverse sequence led to more fatigue and neurotoxicity, thus leading the authors to suggest that the delivery of the taxane first was more tolerable in that relatively small phase II trial.

Finally, one ongoing, randomized phase II trial (NCT00201708) sponsored by the Ohio State University Comprehensive Cancer
Center is assessing whether docetaxel should be administered before or after doxorubicin/cyclophosphamide in a subsequent phase III trial for adjuvant therapy of node-positive breast cancer. The estimated accrual was 56 patients, and the primary end point of this trial is the proportion of patients receiving four cycles of docetaxel with no dose reductions. Chemotherapy cycles are administered every 2 weeks, for a total of eight cycles (four cycles of doxorubicin/cyclophosphamide and four cycles of docetaxel).

**neoadjuvant studies**

Table 2 presents summary information on the eight studies we identified in the neoadjuvant setting, five of which were randomized trials, two were retrospective studies, and one is still ongoing. Once again, the largest study is a retrospective analysis from the M.D. Anderson Cancer Center group [16]. In that study, data from 1414 patients treated in the neoadjuvant setting were used to compare the results among patients treated with paclitaxel followed by fluorouracil, doxorubicin, and cyclophosphamide (FAC/FEC \( n = 226 \)) with those of patients treated with the reverse sequence of FAC/FEC followed by paclitaxel \( n = 1188 \). The corresponding rates of pathologic complete responses \( (pCR) \) with the two sequences were 20.9% and 12.4% \( (P = 0.01) \). In multivariate analysis, after adjustments for period of diagnosis, age, clinical stage, hormone-receptor status, grade, and lymphovascular invasion, the sequence with the anthracycline first was associated with a higher risk of relapse \( (HR = 1.137; P = 0.01) \). These hypothesis-generating results led the authors to conclude that prospective comparisons of the two sequences should be entertained.

In a second retrospective study, Spanish and French investigators reported data on consecutive patients treated with four neoadjuvant cycles of anthracycline-based chemotherapy followed by four cycles of docetaxel \( n = 58 \) or the reverse sequence \( n = 65 \) on 3-weekly schedules [22]. Although there was

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**Table 1. Studies evaluating the role of different anthracycline and taxane sequences in the adjuvant treatment of breast cancer**

<table>
<thead>
<tr>
<th>First author</th>
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CMF, cyclophosphamide, methotrexate, and fluorouracil; FAC, fluorouracil, doxorubicin and cyclophosphamide; FEC, fluorouracil, epirubicin and cyclophosphamide; OSUCC, Ohio State University Comprehensive Cancer Center; RDI, relative dose intensity.

*Target accrual.
no difference regarding the dose intensity of anthracycline between both groups, the dose intensity of docetaxel was significantly higher in the group with the taxane first. Neurotoxicity was also higher in the latter group, which had a lower prevalence of anemia. Although the rate of clinical complete response (66% versus 48%; \( P = 0.045 \)) was higher in the group with docetaxel first, neither the pCR rate, nor the conservative surgery rate, nor the disease-free-survival were statistically different between the two groups.

A prospective pilot study evaluated predictors of response to neoadjuvant chemotherapy in patients with locally advanced breast cancer [23]. Twenty-nine patients were randomized to doxorubicin (90 mg/m\(^2\)) for three cycles followed by paclitaxel (250 mg/m\(^2\)) for three cycles, or the reverse sequence. After the enrollment of the first 20 patients, doses of both agents were reduced (to 60 and 175 mg/m\(^2\), respectively), and the number of cycles of each agent was increased to four in both sequences. Clinical responses were similar in both arms, and a pCR in the breast and lymph nodes was seen in three patients (10%) in the anthracycline-first arm and in two (7%) in the taxane-first arm. No conclusions were drawn by the authors regarding the comparative efficacy of both sequences in this small randomized trial.

Two randomized phase II trials assessed reversed sequences of doxorubicin and a taxane in the neoadjuvant treatment of breast cancer. Miller et al. compared doxorubicin (75 mg/m\(^2\) every 2 weeks for three cycles) followed by weekly docetaxel for six cycles with the reverse sequence in 70 patients and found no statistically significant differences in pCR rates with these regimens (8.6% versus 17.1%) [24]. In a study by the Massachusetts General Hospital group, 54 patients were randomly assigned to receive neoadjuvant doxorubicin (60 mg/m\(^2\) every 2 weeks for four cycles) followed by weekly paclitaxel for nine cycles or the reverse sequence [25]. Once again, there was no significant difference in mean percent decrease in ultrasound tumor volume from baseline to the end of treatment between both arms (79.5% versus 70.6%). Of note, paclitaxel administered before doxorubicin significantly decreased the mean interstitial fluid pressure (IFP) and improved tumor oxygenation, whereas doxorubicin did not produce significant effects on either parameter.

![Table 2. Studies evaluating the role of different anthracycline and taxane sequences in the neoadjuvant treatment of breast cancer (definitions of pathologic complete response varied among studies)](image)
Two phase III trials assessing reversed sequences of an anthracycline and a taxane in the neoadjuvant treatment of breast cancer were recently published. In the Neo-tAnGo trial, 831 patients were randomized in a two-by-two factorial design, with the goals of analyzing the addition of gemcitabine to a backbone regimen of epirubicin, cyclophosphamide, and paclitaxel, as well as the role of sequencing [26]. Patients with tumors ≥2 cm received epirubicin (90 mg/m²) and cyclophosphamide (600 mg/m²) every 21 days for four cycles, followed or preceded by paclitaxel (175 mg/m²) every 14 days for four cycles. A second randomization evaluated gemcitabine combined with paclitaxel. Although the delivered dose intensity was similar across the randomized groups, the pCR rate was significantly higher with the sequence of paclitaxel first (20% versus 15%; P = 0.03), even after adjustments for stratification variables. Long-term progression-free- and overall survival results of this large neoadjuvant trial are awaited. Different results have been found by Buzdar et al., who reported data from the American College of Surgeons Oncology Group neoadjuvant trial Z1041, which addressed the timing of initiation of trastuzumab in operable, HER-2-positive breast cancer [27]. In that trial, 280 eligible women were randomized to four cycles of FEC followed by weekly paclitaxel plus trastuzumab for 12 weeks or the reverse sequence (with weekly trastuzumab throughout the whole chemotherapy treatment). There were no significant differences in pCR rates in the breast (56.5% versus 54.2%) or breast and lymph nodes (48.3% versus 46.7%) between the two arms. However, there were slightly higher rates of grade 3 or 4 treatment-related neutropenia, fatigue, and neurosensory problems in the taxane-first arm.

Finally, our group has started recruitment for a randomized phase II trial that aims at comparing pCR rates and other efficacy end points among patients with HER-2-negative breast cancer treated with three cycles of FEC followed by three cycles of docetaxel or the reverse sequence in a neoadjuvant fashion (NCT01270373). Accrual for this study is ongoing and has a target of 112 patients.

**discussion**

As opposed to the evaluation of the best sequence of adjuvant hormone therapy, something that has been undertaken by a randomized trial with nearly 8000 women and long-term end points [28], studies to date assessing the role of reverse sequences of anthracycline- and taxane-based regimens have been relatively small. A large retrospective study that analyzed close to 1600 patients showed that the usual adjuvant sequence in which an anthracycline was followed by a taxane was associated with a significantly higher risk of death (but not of relapse), when compared with the reverse sequence [16]. The collection of adjuvant trials described herein, with a combined total of nearly 350 patients, showed that the RDI for the taxane was higher, and there were fewer dose reductions when a taxane was administered first. In the neoadjuvant setting, over 1400 patients were analyzed retrospectively and nearly 1300 patients were enrolled in clinical trials, which collectively showed similar or increased pCR rates for sequences in which the taxane was administered first, in comparison with the reverse sequence. The largest randomized phase III trial confirmed the results of the smaller phase II studies, with a statistically and clinically significant difference in pCR rate favoring the taxane-first sequence (20% versus 15%) [26]. After neoadjuvant chemotherapy, pCR is consistently higher in hormone-receptor-negative tumors, when compared with hormone-receptor-positive counterparts. Most studies published to date that compared reversed chemotherapy sequences did not stratify according to hormone-receptor status, and potential imbalances may influence their results. The same goes for HER-2 testing, which was not carried out in most studies [29]. In the pre-trastuzumab era, Stearns et al. showed in a small group of HER-2-positive tumors that the likelihood of achieving a clinical complete response was higher after anthracyclines than after taxanes [23]. A recent trial that added trastuzumab to chemotherapy showed very high pCR rates irrespective of drug scheduling [27]. Therefore, active anti-Her-2 treatments may overcome the impact related to the sequence of chemotherapy agents in this subset of breast tumors.

In essence, none of the trials to date, either in the adjuvant or neoadjuvant setting, has shown disadvantages in terms of efficacy or toxicity for sequences in which the taxane was administered first; the side-effect profile in such trials was related to each specific agent rather than to the sequence used.

The biological rationale for administering taxanes before anthracyclines rests on limited preclinical and clinical observations. Guo et al. [30] assessed the capacity of paclitaxel or doxorubicin to induce cross-resistance to each other and to additional chemotherapeutic agents using cell lines resistant to one of these agents. The selection of MCF-7 breast tumor cells for resistance to doxorubicin generated a population of cells which were >4000-fold cross-resistant to paclitaxel, whereas an identical selection of cells for resistance to the taxane generated a population of cells with only slight (4-fold) cross-resistance to the anthracycline. The exact mechanism for this difference is not completely understood, but seems to be associated with the expression of P-glycoprotein and breast cancer resistance protein. In the study by Taghian et al. [25], the administration of paclitaxel first led to significant differences in IFF and tumor oxygenation, regardless of tumor size or response measured by ultrasound. Such findings raise the hypothesis that tumors undergoing such changes could ultimately have a better overall response because of the improved penetration of the second drug and the improved cytotoxicity of oxygen-dependent drugs (such as doxorubicin and cyclophosphamide). Another potential mechanism refers to senescence, a response to nonlethal stress that results in persistent cytostasis with a distinct morphological and biochemical phenotype; such response is a usual consequence of DNA-damaging agents. Thus, it is possible that doxorubicin-induced senescence may render cells resistant to further therapies, as opposed to the initial treatment with less potent inducers of senescence, such as the taxanes [31, 32]. Finally, a biological observation stemming from an unpublished study indicates a third differential effect of treatment with anthracyclines and taxanes: the analysis of the release of circulating tumor cells after neoadjuvant therapy suggested that longer survival might be achieved by using a taxane followed by anthracycline, compared with the reverse sequence [33].

In the metastatic setting, only a few trials have been designed with the aim of comparing reverse anthracycline and taxane sequences as their primary or secondary objectives [34–37]. The
largest randomized trial to compare drug sequencing was Intergroup trial E1193, in which 739 patients were assigned to receive either single-agent paclitaxel, single-agent doxorubicin, or their combination in the first line; at the time of disease progression, there was a protocol-specified cross-over to the alternative drug in the single-agent arms, which allowed for the secondary comparison of both sequences [34]. The delivery of paclitaxel followed by doxorubicin upon disease progression resulted in no difference in terms of response rate, time-to-treatment failure, or overall survival, when compared with the reverse sequence. French investigators randomized 136 women to one of three arms for total treatment durations of eight cycles: docetaxel alternated with FEC; docetaxel followed by FEC; or the reverse sequence (FEC followed by docetaxel) [37]. The response rate was lower (although not statistically significant so) in the arm with docetaxel followed by FEC, when compared with the two other arms in which docetaxel was administered first. The median time to progression and the 2-year survival rates were similar in the three treatment groups. The authors suggested further investigation for the two regimens with higher response rates. In a smaller randomized trial, the comparison of sequences was a primary aim, as patients received either three cycles of docetaxel followed by three cycles of doxorubicin and cyclophosphamide, or the reverse sequence [35]. Accrual for this study was suspended after 33 patients had been randomized, based on statistical considerations pertaining to trial design. Although median survival times were 2.5 years in the docetaxel-first arm and 1.1 year in the anthracycline-first arm, such difference was not statistically significant, and progression-free survival and objective response rates were similar in both arms. Finally, the sequence with the taxane first appeared slightly less toxic in a randomized phase I trial that compared escalating doses of epirubicin and paclitaxel versus the reverse sequence [36]. It is unknown whether the outcomes of these two trials can be translated into the adjuvant setting. The combination of biological, clinical, and demographic features, as well as the genomic and transcriptomic characteristics of tumors may better tailor the treatment of the individual patient with early breast cancer. Although anthracyclines have been used for decades, validated biomarkers that are able to predict benefit from these agents are currently lacking [38, 39]. Despite encouraging results from some prospective studies [38], several candidate genes have been assessed in studies that were retrospective or confounded by the concurrent administration of other chemotherapeutic agents, thus making it difficult to derive clear correlations between genotype and the effect of anthracyclines [40–43]. Likewise, the contribution of pharmacogenomics to individualizing taxane therapy in breast cancer has been limited to date, and the full potential of gene profiling in early breast cancer is yet to be explored [44–49].

Since the personalized use of specific cytotoxic agents for the (neo)adjuvant chemotherapy of breast cancer remains a clinical challenge, the decision to administer anthracyclines and taxanes in these settings is currently based on classical biological, clinical, and demographic features that are associated with the risks of recurrence. Most adjuvant and neoadjuvant trials have typically incorporated a taxane after the anthracycline-based regimen on the basis of historical evolution, although some recent studies have used the taxane before the anthracycline [12, 50]. To our knowledge, there is no planned or published phase III trial assessing the relative merit of reverse sequences of anthracyclines and taxanes in the adjuvant or neoadjuvant settings. As pointed out by Wildiers et al. [15], it may be difficult to secure funding for a large phase III trial investigating this issue. There are only two registered ongoing phase II trials that compare drug sequencing, and they may provide further information in the adjuvant and neoadjuvant settings, albeit with little power for long-term outcomes. Therefore, given the available information discussed; herein, we believe that a taxane followed by an anthracycline is a sequence option that can be incorporated into daily clinical practice.

[Disclosure]

The authors have declared no conflicts of interest.

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