Sequential Dose-Dense Adjuvant Therapy With Doxorubicin, Paclitaxel, and Cyclophosphamide

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The recognition of paclitaxel's (Taxol's) activity and non-cross-resistance with doxorubicin (Adriamycin) in the treatment of metastatic breast cancer has motivated study of the agent in the adjuvant setting. However, the ideal

Introduction

Despite the application of polychemotherapy, the majority of patients with node-positive early stage breast cancer ultimately experience relapse and die from their disease.[1] Two efforts that aim to increase the curative effect of systemic chemotherapy include increased dose-intensity and inclusion of non-cross-resistant drugs or regimens. Because of paclitaxel's (Taxol) activity and clinical non-cross-resistance with doxorubicin (Adriamycin) in the treatment of metastatic breast cancer, its use in the adjuvant setting is an exciting possibility.[2-5] However, the optimal means of incorporating this drug while maximizing the benefit of the other active agents remains unclear. One approach to applying combination chemotherapy is to simply coadminister two or more active drugs. When synergy occurs, this is a desirable strategy. Unfortunately, concurrent administration is more likely to be associated with increased toxicity than with synergy. Further, the usual strategy for coping with overlapping toxicities is to reduce the dose of the individual drugs. In the case of drugs with a steep dose-to-response relationship, dose reductions are especially undesirable, as they may reduce the effectiveness of the regimen.

To avoid the problem of dose-limiting overlapping toxicities of agents given in combination, non-cross-resistant drugs can be given separately rather than concurrently. In the absence of synergistic cell kill, this is a reasonable approach. Various models have been used to plan the optimal delivery of non-cross-resistant regimens; however, it is the clinical result that should determine the best model for use in subsequent studies.[6-8]

SEQUENTIAL THERAPY: THE MILAN MODEL

An elegant trial from Milan is especially informative, because it compared the use of an alternating regimen with sequential administration. This seminal trial, now reported with a 10-year follow-up, confirmed the prediction of superiority for sequential therapy.[9] In this study, women with metastatic breast cancer, including women with four or more involved nodes, were treated with doxorubicin and cyclophosphamide/ methotrexate/5-fluorouracil (CMF) using one of two schedules: In the alternating-treatment arm, two cycles of CMF were delivered for every one of doxorubicin (symbolized as CCACCACCACCA). In the sequential-treatment arm, all four doses of doxorubicin were given first, followed by all eight doses of CMF (AAAACCCCCCCC).[10] Although it has been speculated that the early use of doxorubicin was responsible for the improved results seen in the sequential-treatment arm, a simpler explanation is that the benefits resulted from the greater dose intensity of doxorubicin achieved with the sequential-delivery approach.[7,11-13] To build on the exciting implications of this study, we performed a follow-up series of clinical trials (Table 1).

DOSE-DENSE THERAPY

Doxorubicin Followed by High-Dose Cyclophosphamide (A→C)

In an attempt to capitalize on the steep dose-to-response relationship associated with alkylating agents while incorporating the demonstrated benefits of sequential therapy, our group evaluated a regimen comprising doxorubicin (Adriamycin) followed by high-dose cyclophosphamide (A→C). In this trial, cyclophosphamide 3,000 mg/m² was given intravenously for three cycles at 14-day intervals, replacing the 24-week regimen of CMF given every 21 days that was used in the earlier
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Milan model. An earlier pilot study conducted in patients with advanced disease[14] prompted use of this dose and schedule of cyclophosphamide, given with G-CSF administered between cycles of cyclophosphamide to facilitate rapid recovery of peripheral blood counts and rapid retreatment. Radiation therapy and tamoxifen were given after chemotherapy in appropriate cases. In 74 patients with breast cancer and a median of nine involved nodes (range, four to 49), our pilot study demonstrated that such a regimen was not only feasible but also had a promising effect on relapse-free survival.[15] A prospective randomized Intergroup trial led by the Southwest Oncology Group is currently testing this treatment approach in patients with zero to three involved lymph nodes.[16]

Sequential Therapy With Doxorubicin/Paclitaxel/ Cyclophosphamide (A\rightarrow T\rightarrow C)
To maximize the potential benefit of paclitaxel as adjuvant therapy, we chose to incorporate the agent into our sequential dose-dense treatment plan with doxorubicin and cyclophosphamide. Given that every model of chemotherapy that assumes fractional cell kill predicts increased effectiveness with more frequent delivery of chemotherapy, we wanted both to shorten the intertreatment intervals between dosing of the three agents[17,18] and to exploit the dose-response relationship demonstrated for doxorubicin.[12] We therefore designed a regimen consisting of doxorubicin (Adriamycin) 90 mg/m², given every 14 days for three cycles, followed first by paclitaxel (Taxol) 250 mg/m² over 24 hours every 14 days for three cycles and then by cyclophosphamide 3,000 mg/m² every 14 days for three cycles (A\rightarrow T\rightarrow C). All nine cycles of chemotherapy were supported by G-CSF, with radiation therapy and tamoxifen as appropriate.

The 42 patients treated had resectable breast cancer with a median of eight involved lymph nodes (range, four to 25). One patient developed disease progression while receiving doxorubicin and was taken off study before receiving paclitaxel and cyclophosphamide. Overall, 69% of the patients required hospitalization (usually for neutropenic fever), and 67% required transfusion of packed red blood cells. Platelet transfusion was required in 10%. Dose reductions of doxorubicin and paclitaxel were required in 10% and 20% of patients, respectively. Despite the extent of toxicity, relapse-free survival was impressive, with only three patients relapsing after just over 1 year of follow-up. We concluded that this regimen was feasible and worth further study, particularly in light of very promising relapse-free survival in patients who had undergone definitive local control surgery.[19]

Previous successful delivery of two cycles of cyclophosphamide 3,000 mg/m² combined with paclitaxel 250 to 300 mg/m², given over 24 hours, suggested that combination of these drugs might be just as feasible as giving them purely by sequential administration.[20,21] Reasoning that we might then be able to treat patients in the adjuvant setting with all three agents over a shorter time period, while maintaining the dose-intensity of the sequential plan, we conducted a randomized phase II trial to prospectively compare the toxicity of this shorter regimen with sequential A\rightarrow T\rightarrow C. As before, treatment began with doxorubicin given every 14 days for three cycles, with G-CSF support. However, because the earlier trial required dose reductions of both doxorubicin and paclitaxel, we started with a lower doxorubicin dose of 80 mg/m². Then, by random assignment, patients were assigned to one of two treatment groups:

- Group A received paclitaxel 200 mg/m² over 24 hours for three cycles, followed by cyclophosphamide 3,000 mg/m² every 14 days for three cycles, again supported by G-CSF.
- Group B received three courses of combination treatment with both agents at the same dose levels.

Thus, half of the patients had nine cycles of chemotherapy (doxorubicin followed by paclitaxel followed by cyclophosphamide), and half had only six (doxorubicin followed by combination paclitaxel/cyclophosphamide), but all received the same total dose of the three study agents. Although follow-up time is insufficient for comparison with previous studies, results of this study showed that the feasibility of the shorter six-cycle regimen was reduced in comparison to the longer, sequential-therapy regimen. Patients had significantly more dose delays, dose reductions, blood transfusions, and hospitalizations.[22] Based on results of this trial, we concluded that the nine-cycle, sequential regimen was preferable for further study.

ONGOING STUDIES
Paclitaxel Plus Doxorubicin
Two European phase II trials[23,24] suggested that paclitaxel plus doxorubicin might provide
additive, if not synergistic, activity. A prospective randomized trial comparing the combination versus either drug alone has been completed but not yet published and promises to clarify the relative advantages and toxicities of the combination versus single-agent therapy with either drug.[25]

To assess the value of this doxorubicin/paclitaxel couplet, and based on the exciting results of their phase II study, the group from Milan has begun a randomized trial to evaluate this combination as adjuvant or neoadjuvant therapy. Patients are randomly assigned to receive high-dose doxorubicin followed sequentially by CMF, similar to the regimen used in the earlier trial from Milan[9], or to receive lower-dose doxorubicin coupled with a 3-hour infusion of paclitaxel, a regimen that appears to be superior in phase II studies of patients with advanced disease. In this trial, patients also have been randomized for the timing of surgery and chemotherapy.

**Doxorubicin/Cyclophosphamide With or Without Paclitaxel**

An alternative means of adding paclitaxel that may avoid the potential for increased toxicity seen in some studies of concurrent dosing is delivery of paclitaxel following administration of the other agents. Two multicenter trials currently under way in the United States take this approach: The first study, led by the Cancer and Leukemia Group B but available through the Intergroup, randomizes patients to receive four courses of A→C using standard, moderately increased, or markedly increased doses of doxorubicin. Subsequently, half of the patients receive paclitaxel and half do not. A second trial of similar design is being performed by the National Surgical Adjuvant Breast and Bowel Project. In this trial, four courses of standard A→C are followed by four courses of paclitaxel, compared with four courses of standard A→C without paclitaxel in women with resected node-positive breast cancer. Taken together, these two trials can be expected to determine the value of adding paclitaxel to A→C as adjuvant chemotherapy for node-positive breast cancer.[16]

**FUTURE DIRECTIONS**

Currently, two prospective randomized trials are under way to test the benefits of high-dose autologous stem-cell-supported chemotherapy for patients with breast cancer involving 10 or more axillary lymph nodes.[16] To compare the efficacy and toxicity of sequential dose-dense therapy with A→T→C versus the more conventional dose-escalated approach, the Intergroup has begun a trial led by the Southwest Oncology Group (SWOG) in women with breast cancer and four to nine involved nodes. Eligible postoperative patients are randomized to treatment with sequential A→T→C as described above or to four cycles of A→C followed by high-dose, autologous stem-cell-supported chemotherapy. Follow-up tamoxifen and radiotherapy are given as appropriate on both arms. Together with the two trials evaluating the simple addition of paclitaxel and the two trials evaluating high-dose chemotherapy, this study should help to further define the role of single-agent paclitaxel in the adjuvant setting and to clarify the relative benefits and toxicities of the dose-dense approach.

**References:**


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