Dose-Dense Paclitaxel-Containing Adjuvant Therapy for Breast Cancer


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The use of dose-dense therapy is one approach to overcoming the “resistance” of malignant cells to adjuvant therapy caused by inadequate drug exposure. In this approach, active drugs are delivered sequentially at their “ideal” dose level separated by short intertreatment intervals. Thus, dose intensification is achieved by means of rapidly recycled treatments rather than by dramatic dose escalation. To overcome absolute cellular resistance, the addition of new, active, non-cross-resistant drugs holds great promise and has specifically motivated the testing of the taxanes. This article describes the results of clinical trials of dose-dense therapy, with particular emphasis on attempts to incorporate one taxane, paclitaxel (Taxol), into the dose-dense regimen of sequential doxorubicin and cyclophosphamide—the so-called A ® T ® C regimen, and into more conventional regimens.[ONCOLOGY 12(Suppl 1)16-18, 1998]

Relapse is common in patients treated for early-stage breast cancer, despite the widespread use of systemic adjuvant treatments, including chemotherapy and hormone therapy.[1] Relapse presumably occurs because of the drug resistance of malignant cells, and efforts to improve systemic therapy are focused on overcoming that resistance. Dose escalation, a strategy to overcome [resistance] in the form of inadequate drug exposure, is promising because of the steep dose-response relationship seen in laboratory models for some of the most widely used chemotherapy agents, such as cyclophosphamide.[2] Another means of overcoming the [resistance] caused by inadequate drug exposure is to apply dose-dense chemotherapy; this approach will be considered in greater detail below. To overcome absolute cellular resistance, ie, the kind of near-complete resistance that may exist at the cellular level against specific drugs, the addition of new, active, non-cross-resistant drugs holds great promise and has specifically motivated the testing of the taxanes (paclitaxel [Taxol] and docetaxel [Taxotere]).[3-5]

Of the two taxanes, paclitaxel has been more extensively studied than docetaxel with regard to dose and schedule, and early reports suggested that it was less toxic.[6] Consequently, initial adjuvant trials were conducted using paclitaxel. More recent evidence suggests that the acute toxicities of docetaxel can be lessened through the concomitant use of several days of steroids, and, therefore, newer adjuvant trials are testing both taxanes.

Dose-Dense Treatment

New active agents have traditionally been incorporated into standard medical oncology practice simply by adding them to existing regimens (ie, drug A + drug B) so as to deliver non-cross-resistant agents as early as possible. This approach was supported by some kinetic models of breast cancer growth and response to therapy (eg, the Goldie-Coldman model). The limitation imposed by this approach is that the doses of simultaneously delivered drugs are usually reduced to avoid overlapping toxicities. Of course, this increases the possibility that some cells that would have been killed by adequate drug exposure will, instead, survive.[2]

If extreme dose escalation does not increase cell kill compared to lower doses, this issue is less relevant, and for some drugs, such as cyclophosphamide, the likelihood of this happening is increasingly supported by clinical studies.[7,8] In such a case, however, the log kill (or fractional cell kill) predictions of earlier models strongly suggest that increased total cell kill is still possible if multiple cycles of therapy are employed.[9] By keeping the time between applications of effective treatments as short as possible, there is less time for cell regrowth.

The net effect of all three of these maneuvers[use of [ideal] (ie, maximally effective) dose rather than maximal dose, repeated cycles, short intertreatment intervals] should be to achieve the greatest possible cytoreduction.[10-12] To reach this goal while minimizing the possibly overlapping...
toxicities associated with the use of multiple non-cross-resistant agents, one could choose to deliver active drugs at their ideal dose level sequentially, so that multiple cycles of drug A are followed by multiple cycles of drug B, and then by drug C, and so on. This approach is termed [dose-dense] therapy because dose intensification is achieved not necessarily or solely through the use of dramatic dose escalation, but rather by means of rapidly recycled treatments.[10]

Clinical Trials
A prospective clinical trial from Milan served as the first [proof-of-principle] in breast cancer that dose-dense therapy could be superior to less dose-dense therapy. In this trial, high-risk patients were randomly assigned to receive either dose-dense therapy, consisting of four sequential cycles of doxorubicin (Adriamycin) followed by eight cycles of CMF (cyclophosphamide, methotrexate, and fluorouracil), or less dose-dense therapy, wherein the CMF and doxorubicin (A) were alternated.[13] The two arms of the trial can thus be represented schematically as AAAACCCCCCCC (or A → CMF) vs CCACCACCACCA. The total drug dose and total time on treatment were identical in the two arms. The rapid recycling characteristic of the sequential plan, however, effectively increases density relative to that achieved with an alternating schedule.

In an attempt to improve on the results obtained with A → CMF, we tested A → C, a regimen in which more dose-dense cyclophosphamide is substituted for the CMF used in the earlier Milan trial. The same dose of doxorubicin (75 mg/m² IV every 21 days for four doses) was followed instead by cyclophosphamide (3,000 mg/m²); cycles were administered at 2-week intervals and supported by granulocyte colony-stimulating factor (G-CSF).[14] This regimen had modest toxicity but was feasible in our pilot study. With a median follow-up approaching 5 years, our group of 71 evaluable women with four or more involved lymph nodes had approximately a 50% relapse-free survival rate.[15]

Integrating Paclitaxel Into Dose-Dense Therapy
To integrate paclitaxel while further exploiting the dose-dense model, we designed the A → T → C regimen, consisting of three doses of doxorubicin (A) (90 mg/m²), followed by three doses of paclitaxel (T) (250 mg/m²/24 h) and then by three doses of cyclophosphamide (3,000 mg/m²). Using 14-day intertreatment intervals and G-CSF support throughout, this regimen consisted of nine cycles of chemotherapy delivered over 18 weeks.

Over a 15-month period, we enrolled 42 otherwise healthy patients with resected breast cancer metastatic to four or more axillary nodes into a trial of this regimen. As expected, toxicity was significant, with 69% of patients admitted at least once to the hospital, usually for neutropenic fever, and 67% requiring at least one transfusion of packed red blood cells.[16] However, there were no deaths, and the preliminary results of this trial are excellent, with 81% of patients remaining free of disease at a median follow-up of more than 3 years.[15]

Modifications of the Regimen
Because the high incidence of hematologic toxicity could limit the applicability of this regimen, we next studied several modifications to the A → T → C regimen. The dose of doxorubicin was lowered to 80 mg/m², the paclitaxel dose was decreased to 200 mg/m² (still infused over 24 hours), and patients were randomized to sequential paclitaxel (T) + cyclophosphamide (T → C) or concurrent paclitaxel (T) + cyclophosphamide (T + C).

The T + C combination had previously been found to be feasible in other disease settings at our institution but had not been tested following doxorubicin.[17] If feasible, this approach (A → T + C) offered the possibility of shortening the regimen by three treatment cycles to 12 instead of 18 weeks, without compromising the total drug dose or dose intensity. As before, intertreatment intervals were 14 days and all cycles were supported by G-CSF.

With less than half of the planned patients randomized, the superior feasibility of the nine-cycle sequential regimen was statistically and clinically obvious. It delivered greater dose and dose-intensity with lesser toxicity by every parameter.[18] Indirect comparisons to the earlier A → T → C regimen also suggested a marked reduction in toxicity with the use of the slightly lower starting doses. Therefore, we closed this trial early, concluding that sequential A → T → C was preferable for further study.

Randomized Trials
The first, large, randomized trial of A → T → C is being conducted within the Intergroup with SWOG as the lead organization. Eligible patients must be otherwise healthy and have undergone surgery for...
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breast cancer metastatic to four to nine nodes. By random assignment, 1,000 patients will receive either A → T → C (doxorubicin [A] 80 mg/m² for three doses; paclitaxel [T] 200 mg/m²/24 h for three doses; and cyclophosphamide 3,000 mg/m² for three doses; all at 14-day intervals with G-CSF support) or AC (doxorubicin, 80 mg/m² for four doses; and cyclophosphamide, 600 mg/m² for four doses; both at 21-day intervals) followed by either the Solid Tumor Autologous Marrow Program (STAMP) I or V high-dose chemotherapy regimens. Both STAMP I and V are supported by G-CSF plus infusion of peripheral blood stem cells harvested following the final administration of AC. Because this trial directly compares the two most promising, dose-intensive approaches previously piloted in high-risk early-stage breast cancer, it should effectively guide the course of future research and clinical practice in this patient subset.

Other trials of A → T → C are under way or under consideration. One trial, planned for the Intergroup and led by the Cancer and Leukemia Group B (CALGB), randomizes patients into four arms consisting of A → T → C or AC → T at 2- or 3-week intertreatment intervals.[Mark Citron, md, personal communication, May 1997] This study will help determine the value of the 33% increase in dose intensity afforded by 14-day intertreatment intervals, as compared to 21-day intervals. In addition, it will determine whether combination therapy using AC → T is more or less toxic than sequential therapy using A → T → C.

Summary

The possibility that taxanes will improve on the results of existing adjuvant chemotherapy regimens remains to be proven but should be adequately addressed by the generation of clinical trials now nearing completion and analysis. Typical of these are the CALGB and National Surgical Adjuvant Breast Project (NSABP) trials of AC with or without subsequent paclitaxel or docetaxel. Both of these trials consist of AC for four cycles, followed by paclitaxel for four cycles vs observation. Regardless of the results of these trials, we will still need to identify the optimal means of incorporating paclitaxel into adjuvant therapy in terms of dose (175 mg/m², 250 mg/m², or other), infusion length (3-hour, 24-hour, or other), schedule (1-, 2-, or 3-week intervals) and treatment plan (single agent or combination therapy).

Based on preliminary results of nonrandomized trials, the use of sequential dose-dense A → T → C holds great promise, but this promise must be confirmed by phase III studies. Such trials, along with the wide array of studies testing other dose, schedule, and treatment plan options, should adequately steer us closer to the [best] adjuvant treatment approach for the near future. Participation by all oncologists in these trials will speed this process and allow us to optimize adjuvant therapy as soon as possible for all patients whether treated on or off a study.

References:


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