Current and Planned Trials With Capecitabine in Adjuvant/Neoadjuvant Therapy of Breast Cancer

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The demonstration of the activity of capecitabine (Xeloda) in advanced breast cancer and of the ability of capecitabine/docetaxel (Taxotere) to improve tumor response, time to disease progression, and survival in this

1There is considerable rationale for evaluating the combination of capecitabine (Xeloda) and a taxane in the adjuvant setting in breast cancer. Capecitabine is activated by thymidine phosphorylase, which exists in higher concentrations in tumor tissues. Taxanes have been shown in preclinical systems to upregulate thymidine phosphorylase, which would result in the accumulation of higher tumor concentrations of capecitabine. The expectation of increased antitumor activity has been borne out in a recent phase III trial showing that docetaxel (Taxotere)/capecitabine resulted in significant improvement in tumor response, time to disease progression, and overall survival compared with docetaxel alone in anthracycline-pretreated stage IV disease.[1] These positive results and the promise of significant antitumor effects have prompted the design of numerous studies assessing capecitabine in combination with a taxane or alone in adjuvant or neoadjuvant therapy.

Rationale

Several years ago, investigators at the University of Washington, Seattle, developed a program of continuous chemotherapy to supply dose-dense treatment, primarily involving doxorubicin and cyclophosphamide (Cytoxan, Neosar). The rationale for such an approach consisted of several observations. First, weekly administration of doxorubicin produces cytotoxic concentrations of the drug that persist for several days (formerly believed to be about 4 to 5 days, now recognized as about 2 to 3 days). Second, daily administration of cyclophosphamide produces continuous cytotoxic concentrations of active metabolites. Third, human solid tumors have a turnover that is relatively slow (ie, compared with that observed in mouse models), and may thus be more responsive to treatment focused on providing active drug concentration for prolonged continuous time periods (ie, the dose-dense approach) than to treatment focused on providing higher concentrations more intermittently. Fourth, it was observed that "metronomic" cyclophosphamide exerts an antitumor effect independent of cytotoxicity in some preclinical breast cancer models (ie, when the cell line was resistant to cyclophosphamide); these and other findings have suggested that metronomic/continuous treatment with cyclophosphamide might exert an antiangiogenic effect. These considerations prompted the performance of pilot studies to assess the effects of continuous, dose-dense treatment with fluorouracil (5-FU), doxorubicin (Adriamycin), and cyclophosphamide (FAC) in node-positive primary breast cancer. The first 30 patients treated (first study) received 5-FU at 300 mg/m²/wk, doxorubicin at 20 mg/m²/wk, and cyclophosphamide at 60 mg/m²/d for 24 weeks; patients received granulocyte colony-stimulating factor (G-CSF [Neupogen]) 6 days per week (FAC+G). A high rate of grade 2 hand-foot syndrome (57%) in these first 30 patients led to removal of fluorouracil from the regimen. The next 23 patients treated (second study) received a regimen of doxorubicin at 24 mg/m²/wk for 20 weeks (total dose of 480 mg/m², as in the first 30 patients) and cyclophosphamide at 60 mg/m²/d; these patients also received G-CSF 6 days per week (AC+G). Erythropoietin therapy was added to treatment shortly after the first study was begun; all 23 patients receiving AC+G received weekly erythropoietin treatment. No taxane consolidation was used. Patients with estrogen receptor (ER)-positive status received tamoxifen (Nolvadex) treatment. Overall, patients had a median of 4 positive nodes (range: 1 to 22) and 18 (43%) of the 43 evaluated for HER2/neu receptor status were HER2/neu-positive.
The target dose intensity of doxorubicin was 15 mg/m²/wk, based on findings in a Cancer and Leukemia Group B (CALGB)/Intergroup trial indicating an advantage of planned dose intensity of this level over lower planned dose intensities.[2] Mean weekly doses of doxorubicin were 18.8 mg/m² (median: 18.5 mg/m², range: 12 to 24 mg/m²) in all 53 patients, 17.7 mg/m² (median 17.6 mg/m², range: 12 to 21 mg/m²) in the 30 FAC+G patients, and 20.1 mg/m² (median: 21 mg/m², range: 14 to 24 mg/m²) in the 23 AC+G patients. Grade 3 toxicities consisted of neutropenia in 22% to 30%, anemia in 0% to 17%, nausea/vomiting in 0% to 10%, hand-foot syndrome in 4% to 7%, and stomatitis in 3% to 13%. Grade 4 toxicities consisted of neutropenia in 10%, with 3% of patients requiring hospitalization for febrile neutropenia, and anemia in 0% to 3%.

Patients had a median follow-up of 64 months (range: 8 to 100 months). At 5 years, disease-free survival among the total group was 85%, with an apparent plateau in the survival curve after 5 years (Figure 1). Informal comparison of this outcome with 5-year event-free survival rates (62% to 65%) in earlier National Surgical Adjuvant Breast and Bowel Project (NSABP) trials using standard AC as control treatment in node-positive patients suggests a marked improvement with the continuous therapy approach (Table 1).[3,4] This difference in outcome does not appear to be related to reduced nodal involvement, as the current study population had a smaller proportion of patients with one to three positive nodes and a greater proportion with four to nine positive nodes.

In addition to these findings, a Seattle/Southwest Oncology Group (SWOG) study[5] in patients with stage III/inflammatory breast cancer showed that an identical continuous AC+G regimen produced a 24% pathologic complete response rate and a 50% major pathologic response rate overall. A SWOG randomized trial comparing continuous AC+G with standard AC in patients with locally advanced and inflammatory breast cancer is ongoing.

**Trials of Capecitabine in the Adjuvant Setting**

Several groups have planned or initiated trials to assess the effects of capecitabine in adjuvant or neoadjuvant therapy.

**US Oncology Trial**
In a trial to be performed by US Oncology, patients with resected stage II breast cancer are to be randomized to standard AC for four cycles, followed by docetaxel for four cycles; or to standard AC for four cycles, followed by docetaxel/capecitabine for four cycles (Figure 2).

**NSABP Trial**
In another trial of similar design planned by NSABP in the neoadjuvant setting, patients with operable breast cancer are to be randomized to standard AC for four cycles, docetaxel for four cycles, and surgery; or to standard AC for four cycles, docetaxel/capecitabine for four cycles, and surgery (Figure 3).

**M. D. Anderson Trial**
In an adjuvant/neoadjuvant trial conducted at the University of Texas M. D. Anderson Cancer Center, patients with stage I to IIIA disease in the adjuvant setting or stage IIA to IIIA disease in the neoadjuvant setting are to be randomized to weekly paclitaxel for 12 cycles or capecitabine/docetaxel for four cycles, with both arms then receiving 5-FU/epirubicin (Ellence)/cyclophosphamide (FEC) for four cycles followed by surgery or radiation therapy; patients with ER-positive tumors are to receive endocrine therapy (Figure 4). The selection of weekly paclitaxel for the initial single-agent taxane arm is based on findings of a recent trial showing that weekly paclitaxel was superior to paclitaxel every 3 weeks when all patients subsequently received identical FEC therapy.[6] The pathologic complete response rate was doubled, from 14% to 28%, on the weekly arm.

**CALGB Trial**
Finally, CALGB study 49907 is to assess adjuvant therapy in patients 65 years or older with node-positive or high-risk node-negative disease. Patients are to be randomized to either standard AC for four cycles or cyclophosphamide/methotrexate/5-FU for six cycles depending on investigator preference vs capecitabine for six cycles (Figure 5).

**Conclusions**
The activity exhibited by capecitabine in breast cancer and the results achieved in advanced disease with the capecitabine/docetaxel combination suggest a number of approaches to using this interesting drug in the adjuvant and neoadjuvant settings. At the same time, accumulating evidence that continuous, dose-dense AC or FAC treatment may provide better outcomes than standard regimens indicates the need to examine this approach in the adjuvant setting. Trials are planned to
assess capecitabine in combination with docetaxel or alone in adjuvant or neoadjuvant treatment. Findings in these trials should provide important information on the range of uses of capecitabine in treating breast cancer.

References:


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